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THE VENTILATORY FUNCTION OF THE LUNG IN EMPHYSEMA AND ASTHMA*

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This study of emphysema and asthma was undertaken with the idea that great changes in the dead space must occur when an emphysematous patient suffered an asthmatic attack.

It was suggested in a former publication on emphysema[1] that the dead space was probably much enlarged in emphysema. If this were true then the dead space of an emphysematous patient must undergo a great change during an attack of asthma. We have succeeded in getting two emphysematous patients who had frequent attacks of asthma. After some persuasion, these patients learned to breathe through the Zuntz apparatus during asthmatic attacks. The asthma of both patients could always be relieved by subcutaneous injections of epinephrin. In this way we had numerous opportunities to compare the minute volume of air and the alveolar air of the emphysematous state with the asthmatic state. Much to our surprise we found the dead space, as measured by our method, varied little in the two conditions. Furthermore, we found the minute volume remained nearly the same, the concentration of carbon dioxid in the alveolar air was increased very little during the asthmatic attacks, but in spite of these slight variations in lung ventilation the patients commonly were cyanotic during the attacks of asthma and we could not account for cyanosis by any changes in the circulatory system.

To produce cyanosis by impairment in the circulation, the evidences of stasis must be very great. Sufficient stasis may occur to cause air hunger, marked cardiac enlargement and pronounced stasis in the venous system as evidenced by widening of the jugular veins and hepatic enlargement, and, in spite of all these signs, cyanosis may not be apparent.

The problem then presents itself in this wise. An emphysematous patient may have an attack of asthma which will modify the measur-

* Submitted for publication, July 23, 1914.

1. Hoover, C. F.: The Minute Volume and Alveolar Air in Pulmonary Emphysema, THE ARCHIVES INT. MED., 1913, xi, 52.

able lung ventilation very little and not cause any demonstrable changes in the circulation, but cyanosis commonly occurs. What may then account for the cyanosis? Some alteration in the function of external respiration owing to changes in the respiratory membrane during asthma? Or is there some factor in lung ventilation which we have thus far failed to take into account?

From our observations we have come to the conclusion that certainly a factor thus far unrecognized in lung ventilation is one cause, and, possibly, changes in the respiratory membrane during asthma may be another cause of cyanosis in asthma.

As was stated, when we began our observations we sought to compare the dead space of asthma with the dead space of emphysema, but our results failed to show any essential change in the size of the dead space. Sometimes the results showed a larger dead space in asthma and at other times the results were reversed. At no time was the change in the dead space sufficiently large to have any significance. Our method was to collect specimens of the expired air and measure the minute volume of air, and also procure specimens of alveolar air during the asthmatic attacks, then we repeated these procedures directly after the asthma was relieved. It is obvious that the entire carbon dioxid is contained in the alveolar air and the air of the dead space will contain no carbon dioxid. At least this is true for an instant at the end of an inspiratory effort. With expiration the alveolar air and dead-space air are expelled together, but the air at the end of the expiration will be free of dead space air, so by knowing the carbon dioxid content of the total expired air and the carbon dioxid percentage in the alveolar air we can easily estimate the total amount of alveolar air. Therefore, the dead space will equal the total expired air minus the alveolar air. If, for instance, a total expiration equals 1,000 c.c. and its carbon dioxid content equals 5 per cent. and the carbon dioxid content of the alveolar air equals 5.5 per cent., then the total alveolar air equals

$$\frac{0.05 \times 1{,}000}{0.055} = 909 \text{ c.c.}$$

therefore the dead space is $1.000 - 909 = 91$ c.c.

It is clear, then, that the dead space estimated in this manner will depend on the volume of expired air and the disparity between the carbon dioxid content of the expired air and the carbon dioxid content of the alveolar air. In our observations on asthmatic patients we employed the Zuntz method, which is not sufficiently accurate for estimating the dead space, but it is accurate enough for comparative studies of the ventilatory function of the lung.

The minute volume specimens of air collected with the Zuntz apparatus are supposed to be collections composed of very minute

parts of each expiration. If a specimen of 50 c.c. is collected from a patient breathing fifteen times a minute for ten minutes and each expiration equals 800 c.c., then it must be assumed that from each expiration of 800 c.c., 0.33 c.c. of air enters the collecting tube. Therefore, to be a perfect sample of the expired air, this 0.3 c.c. of air must be composed of the same proportions of air from the dead space and the alveolar air which are represented in the total expiration of 800 c.c. This cannot be expected, because the air of an entire expiration is not delivered with the same pressure throughout the entire expiratory phase, and if the pressure of expiration plays any part in the displacement of the liquid in the sampling-tube there will be more displacement in the first part of an expiration than in the latter part. The turning of the spindle of the spirometer is therefore not the only factor which may cause replacement of the contained fluid with air. Were the revolving spindle the only factor to replace the fluid with air in the sampling-tube there is another source of error, whether mercury or acidulated water is used in the tube. The discharge of the fluid is in drops and not in a graduated stream of minute proportions as should occur if the sample of air is to be a collection of the total expired air in miniature, consequently air replaces each drop as it escapes from the tube, and it is a mere chance at just what part of expiration this replacement of liquid by air takes place. The results are fairly constant, but when a sample of air obtained with the Zuntz apparatus is compared with the total expired air collected in a rubber bag it is found the Zuntz specimens have a lower carbon dioxid content. We take this to be evidence that a disproportionately large part of the first portion of each expiration is captured in the sampling-tube, as this portion of an expiration is delivered under higher pressure than is the latter portion of an expiration; and the first part of an expiration has a lower carbon dioxid content than the latter part. For this reason the dead space is reckoned larger when the Zuntz apparatus is used than when the entire expiration is captured and compared with the alveolar air. When the Zuntz apparatus was used, Patient R. J. gave the following result:

Minute volume equals .....9,000 c.c.
Respiratory rate equals.....21 per minute
Each respiration equals.....428 c.c.
Carbon dioxid in alveolar air equals..5.2 per cent.
Carbon dioxid in expired air equals...1.9 per cent.

When the rubber bag was employed to collect the minute volume or total expired air:

Minute volume equals.....9,000 c.c.
Respiratory rate equals.....24 per minute
Each respiration equals.....425 c.c.
Carbon dioxid in alveolar air equals..5.0 per cent.
Carbon dioxid in expired air equals..3.58 per cent.

From many estimates made by the two methods during different periods of our studies it is quite clear that specimens of the total expired air collected by the Zuntz apparatus give too low a percentage of carbon dioxid.

The first question to be settled is whether stenosis of any and all parts of the air-passages will cause an increased volume of the affected lung area.

That the lung increases in volume during bronchiolar spasm is perfectly clear, but bronchiolar spasm may carry with it some other factor than mere stenosis of the air-passages.

During the past year, one of us saw a child with laryngeal diphtheria which caused marked stenosis of the larynx, but the stenosis was not severe enough to cause cyanosis. There was descent of the lower lung borders and also descent of the entire diaphragm, as was clearly proved by strong inspiratory narrowing of the subcostal angle.

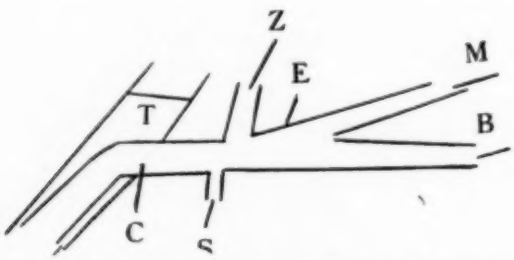

Diagram of cannula by which samples of air were taken for analysis. *T*, trachea; *C*, cannula; *Z*, branch to Zuntz apparatus; *S*, lateral opening for sampling air; *M*, branch of mercury manometer; *B*, branch to bottle of 2,540 c.c. capacity; *E*, clamp.

We also employed some animal experiments to prove the same point. Dogs were first anesthetized with ether and then (after tracheotomy) a cannula was securely fixed in the trachea. The dogs were then given a sufficiently large dose of morphin so they would lie quietly breathing through a Zuntz apparatus. In the cannula a lateral opening was made 1 inch from the trachea, through which samples of air could be taken by sampling-tubes which were previously exhausted for the purpose.

The cannula had two branches, one of which led to the Zuntz apparatus and one branch terminated in a Y tube. One branch of the Y connected with a mercury manometer and the other branch connected with a bottle of known capacity.

A screw clamp was applied to the tube *Z*, which enabled us to produce any desired amount of stenosis.

While the animal was breathing, *S* was closed and a clamp applied at *E*, so the animal breathed only through the Zuntz apparatus.

The bottle to which the tube *B* was connected was then exhausted and the amount of minus pressure in the bottle was accurately measured on the mercury manometer.

When a specimen of alveolar air was wanted, the tube *Z* was clamped at the end of an inspiration. At the same moment the tube *M* was clamped and the clamp at *E* was released. As the signal was given an assistant compressed the animal's thorax and abdomen so the air contained in the lung was aspirated into the bottle as all other communications were closed. During the aspiration it was necessary to clamp the tube *M* to prevent the churning of air by the oscillations of the mercury column. The dog's thorax was also compressed from without during the aspiration process to prevent rupture of the lung, which we found in our first experiments caused pneumothorax.

When the aspiration was completed the clamp at *E* was replaced and the clamps at *M* and *Z* were released, so the animal continued breathing through the Zuntz apparatus.

By measuring the change in the stand of the mercury manometer before and after aspiration we could readily estimate how much air was drawn out of the lungs into the bottle.

By using the same minus pressure in the bottle, we were able to compare the amount of air yielded when there was stenosis, with the amount of air yielded under the same aspiration when there was no stenosis in the respiratory path.

This apparatus was designed for the purpose of getting specimens of alveolar air from dogs. Incidental to these experiments, however, the following observations were made in an experiment designed to measure and analyze the minute volume of air and also to estimate the carbon dioxid content of the alveolar air.

Specimens of alveolar air were procured before a stenosis was produced and also during the period of stenosis. The pressure in the bottle was the same when all the specimens were taken, namely, 290 mm. Hg less than barometric pressure.

Without stenosis, three aspirations yielded 346, 242 and 340 c.c.

With stenosis, three aspirations yielded 405, 610 and 534 c.c.

The increase in the lung volume was not sufficient to cause inspiratory narrowing of the subcostal angle. The subcostal angle distinctly widened during inspiration in the period of stenosis.

Therefore, the increase in the residual air of the dog's lungs was proportionately much smaller than was the increase of residual air in the child who had laryngeal stenosis. We believe we are justified in

arriving at this inference from former comparative observations on the movements of the costal borders in dogs and in human beings.[2]

The patient R. J. exhibited signs during an asthmatic attack which are of interest in this relation. During the night of Aug. 30, 1913, R. J. had an attack of asthma which gave him as much discomfort as any other attacks, but the asthma was confined to the upper left and lower right lobes. The air-hunger was intense and there was both inspiratory and expiratory dyspnea. Coarse râles were abundant over the entire thorax, but fine whistling râles during inspiration and expiration were confined to the upper left and lower right lobes. It was also observed that the right costal border was strongly drawn toward the median line during inspiration, but the left costal border was drawn away from the median line.

Thus far it seems clear we are justified in saying that stenosis anywhere in the tracheobronchial system will cause an increase of the residual air in that part of the lung supplied by the affected air-passages.

This experience also indicates that the excitatory influence operates locally on the affected bronchial system and not by way of the blood-stream. If bronchiolar constriction were accomplished by absorption of split products of proteid into the blood-stream, it is not probable we could have regional bronchiolar constriction with regional increase in pulmonary volume.

The problems of emphysema and asthma are more complicated than first acquaintance would lead one to believe. We can understand how an emphysematous patient may have a bronchiolar spasm and thus contribute to an increase of the residual air; and also, that the same minute volume of respired air with the same respiratory rate will be less effectual than in the non-asthmatic periods.

If the residual air is much increased, then of course the ventilation must be enlarged to maintain a sufficient reduction in the carbon dioxid concentration of the alveolar air. That a greatly increased effort at respiration must be expended by the patient to accomplish this ventilation is clear enough to any one who watches a patient during an attack. When an emphysematous patient has an attack of asthma the minute volume of air and respiratory rate may be unaltered and, indeed, as we will show, the minute volume may be as large as during the interims of comparative comfort, but in spite of the ventilation the patient will be cyanotic during the attack and the carbon dioxid concentration of the alveolar air increases. Whether or not all these facts can be explained by increase of residual air remains to be seen.

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2. Hoover, C. F.: The Functions of the Diaphragm and their Diagnostic Significance, THE ARCHIVES INT. MED., 1913, xii, 214.

CASE 1.—The patient, Mrs. L., was admitted to Lakeside Hospital in April, 1913. The case represented the usual type of emphysema with bronchitis and asthma. Bronchitis existed a year before admission, but asthmatic attacks occurred only a few months before admission.

The tongue, nose, ears and finger-nails showed no cyanosis, although the lips suggested a slight cyanotic tinge. Sputum was abundant and contained many cellular elements. About 40 per cent. of the cells took the acid stain, but the granules of the cells did not have the conformation of the granules of eosinophils. The cells had the appearance of polymorphonuclear cells stained red instead of the usual neutral color.

Curschmann spirals and Charcot crystals were present in great abundance.

Between the attacks, the lungs were sufficiently large to fill the pleural sinuses, but there was distinct inspiratory widening of the subcostal angle.

During the day of April 12, 1913, two specimens of alveolar air were taken and found to contain 5 and 4.55 per cent. of carbon dioxid.

On the night of April 12 the patient had a severe attack of asthma with slight cyanosis. The alveolar air in two specimens contained 5.43 per cent. and 5.3 per cent. of carbon dioxid.

Fifteen minims of epinephrin solution 1:1,000 (adrenalin P., D. & Co.) were then given subcutaneously and in two minutes the air-hunger was relieved and the inspiratory narrowing of the subcostal angle changed to distinct inspiratory widening of the angle. The lower borders of the lung remained the same. Two specimens of alveolar air were then taken and found to contain 4 and 4.10 per cent. of carbon dioxid.

After a number of trials Mrs. L. learned to breathe through the Zuntz apparatus during her asthmatic attacks. We had the opportunity to collect specimens of the minute volume and alveolar air during five attacks of asthma. All the attacks were relieved by the subcutaneous injections of epinephrin so we had the opportunity to compare the lung ventilation and alveolar air during the attacks, with specimens procured directly after the asthma was relieved.

The results obtained on the night of May 1, 1913, are very characteristic and serve to illustrate the question under discussion.

The asthmatic attack was severe. The patient was awakened out of her sleep with air hunger and noisy respiration. Cyanosis was perceptible in the finger-nails and ears and lips. The subcostal angle narrowed during inspiration. The pulse was 100 per minute, respiration 28 per minute, blood-pressure 130 systolic and 90 diastolic.

Four specimens of alveolar air were then taken with the following results: Carbon dioxid, 5.37 per cent.; 5.14 per cent.; 5.20 per cent.; 5.50 per cent.

Immediately after these specimens were taken, a specimen was procured with the Zuntz apparatus.

Time equals .....seven minutes
Minute volume equals .....5.06 liters
Respiration rate equals.....20 per minute
Carbon dioxid equals.....2.6 per cent.

A second Zuntz specimen was taken with the following result:

Time equals .....six minutes
Minute volume equals.....5.2 liters
Respiratory rate equals.....19.8 per minute
Carbon dioxid equals.....2.74 per cent.

One hour after the onset of the attack 15 minims of epinephrin solution 1:1,000 given subcutaneously without clearly perceptible improvement in the symptoms. Twenty minutes later 15 minims of epinephrin 1:1,000 were again given subcutaneously. A few minutes later the asthma subsided and the costal angle changed from narrowing to widening during inspiration.

A Zuntz specimen was then taken.

Time equals .....eight minutes
Minute volume equals.....6.4 liters
Respiratory rate equals.....17.6 per minute
Carbon dioxid equals.....2.0 per cent.

Three specimens of alveolar air were then taken with the following results: Carbon dioxid, 5.2 per cent., 5.07 per cent., 5.01 per cent.

In all the experiments tried on this patient there was not sufficient change in the minute volume of air and carbon dioxid concentration during the attacks of asthma to account for cyanosis. It seems there must have been some other factor besides a change in the ventilatory function of the lung to account for cyanosis during the attack of asthma.

Case 2.—Patient, R. J., a colored man, aged 30, had emphysema, bronchitis and asthma during four years before entering Lakeside Hospital. During July, 1913, R. J. had twelve attacks of asthma which were relieved by subcutaneous injections of epinephrin. During August the attacks continued much the same.

August 29, specimens were taken when the patient was breathing very comfortably, although he had an asthmatic attack the previous night. Four specimens of alveolar air were taken and gave a carbon dioxid content of 6.6 per cent. 6.5 per cent., 6.9 per cent. and 6.3 per cent. The respiratory rate was 16 per minute; minute volume was 9.180 liters.

Aug. 30, 1913, R. J. had a severe attack of asthma with intense air hunger. During the asthma the alveolar air gave the following result in carbon dioxid: 7.1 per cent., 7.9 per cent., 7.6 per cent. The respiratory rate was 25.6 per minute; minute volume was 9.570 liters.

This attack began at 7 p. m. At 7:29 p. m., 15 minims of epinephrin were given subcutaneously. Air hunger ceased very suddenly at 7:34 p. m. Alveolar air specimens, taken directly after asthmatic breathing ceased, had the following content of carbon dioxid: 6.1 per cent., 5.7 per cent. and 6.2 per cent. The respiratory rate was 21 per minute. The minute volume was 9.6 liters.

The notable fact in this observation is that during the asthmatic attack the minute volume was nearly as large as when the attack was over and the respiratory rate was increased only four per minute during the attack. During the asthmatic period there was cyanosis of the tongue.

Sept. 4, 1913: Asthma severe, loud whistling râles during inspiration and expiration throughout the lungs. The subcostal angle narrows during inspiration. Three alveolar air specimens had a carbon dioxid content of 5.7 per cent., 6.6 per cent. and 6.6 per cent.

Two Zuntz specimens were taken during the attack of asthma with the following results: 1. Time, five minutes; respiratory rate, 24.2 per minute; minute volume, 6.610 liters. 2. Time, five minutes; respiratory rate, 22 per minute; minute volume, 6.58 liters.

After the preceding specimens were taken, 20 minims of 1:1,000 epinephrin were given subcutaneously and relief followed immediately.

Two specimens of alveolar air were then taken and they contained 5 per cent. and 5.9 per cent. of carbon dioxid.

A Zuntz specimen (taken directly after the attack) gave the following:

Minute volume equals.....7.772 liters
Respiratory rate equals.....23 per minute
Carbon dioxid equals.....1.54 per cent.

The attack of September 4 was particularly severe and the patient's suffering was intense, but judging from the pulmonary ventilation and the carbon dioxid content of the alveolar air one is at a loss to account for the source of cyanosis, for during the attack the carbon dioxid content of the alveolar air was raised only 0.6 per cent. and the minute volume was diminished only

one liter. This increase of the carbon dioxid concentration with the lowered minute volume and increased residual air, may account for great discomfort, but these factors do not account for cyanosis during the attack.

Sept. 18, 1913, R. J. had an asthmatic attack of moderate severity. The lower lung filled the pleural sinuses and the subcostal angle narrowed during inspiration, but there was no cyanosis.

During the attack two Zuntz specimens were taken.

1. Time, four minutes; minute volume, 9.790 liters; respiratory rate, 25 per minute.

2. Time, five minutes; minute volume, 9.870 liters; respiratory rate, 25.6 per minute.

Two specimens of alveolar air contained 5.96 per cent. and 5.65 per cent.

Epinephrin given subcutaneously relieved this attack in less than one minute. The subcostal angle widened during inspiration.

Two Zuntz specimens then taken gave the following results:

1. Time, three minutes; minute volume, 9,000 liters; respiratory rate, 21.6 per minute.

2. Time, five minutes; minute volume, 8.790 liters; respiratory rate, 22 per minute.

3. The three alveolar specimens gave the following in content of carbon dioxid: 5.22 per cent., 4.74 per cent. and 5.44 per cent.

October 12, R. J. had a severe attack of asthma with cyanosis.

Two Zuntz specimens were taken. Results were:

1. Time, six minutes; minute volume, 7.04 liters; respiratory rate, 25.5 per minute.

2. Time, five minutes; minute volume, 7.37 liters; respiratory rate, 26.4 per minute.

Two alveolar air specimens gave content of carbon dioxid: 8 per cent. and 6.88 per cent.

The specimens given above are some of the most satisfactory we could procure from these patients. Although we do not believe the Zuntz method has proved to be satisfactory for accurate studies of the carbon dioxid content of expired air, the results are valuable for comparing asthmatic breathing with the breathing during interims of comfort.

The results show that during asthmatic attacks the minute volume of air and respiratory rate may be little altered. The difference would be scarcely enough to cause discomfort in a normal person. It was also observed that the percentage of carbon dioxid in the alveolar air was not much increased, but the increase in percentage of carbon dioxid in the alveolar air was much greater than the difference in the minute volume would allow.

Provided that the minute volume of air remained unaltered, there would be a rise in the carbon dioxid concentration of alveolar air because the residual air is increased, and for this reason the same volume of ventilation would cause less reduction in the concentration of carbon dioxid in the alveolar air. We find, however, that the dilution of residual air is not directly proportioned to the amount of air inhaled.

If we assume the residual air in the lungs of a normal person to be about 2 liters we are justified in assuming that at the end of a forced expiration the residual air is constant in amount. In a large number of observations on a healthy man, G., it was found if a forced expiration was made and then followed by a maximum inspiration and a forced expiration, and the total expired air was measured, the total expiration did not vary more than 300 c.c. in any of the trials.

If the maximum ventilation remains constant then we are justified in assuming that the amount of alveolar air in the lungs and bronchial tree at the end of a maximum expiration will be the same or very nearly the same.

We found in G. that the amount of carbon dioxid eliminated per minute when he was at rest varied between 415 and 430 c.c. (moist).

While breathing tranquilly, seated, G. made a forced expiration lasting one second. The alveolar air at the end of the expiration contained 6.06 per cent. carbon dioxid. G. then inspired two seconds and then made a forced expiration lasting two seconds.

The total expiration was captured and a specimen of the end alveolar air was taken at the same time. Briefly stated, the following results were obtained:

Expiration, one second, alveolar air equals	6.06 per cent. carbon dioxid
Inspiration	two seconds
Expiration, two seconds, alveolar air equals	5.80 per cent. carbon dioxid
Total alveolar air equals	735 c.c.
Dead space equals	140 c.c.
Total expiration equals	875 c.c.
Carbon dioxid content equals	4.88 per cent.

During the four seconds occupied in the inspiration and expiration 27.8 c.c. of carbon dioxid were secreted.

Assuming there was no carbon dioxid secreted during the four seconds and also taking 2,000 c.c. for the residual alveolar air, at the end of the first expiration there must have been a minimum of (2,000 + 140) c.c. times 6.06 per cent. of carbon dioxid in the alveolar air and dead spaces.

At the end of the inspiration the alveolar air in the lung with its carbon dioxid dilution can then be expressed by $2{,}000 + (875\text{-}140)\ x$.

We then have the following formula:

$$2{,}140 \times 6.06 \text{ per cent.} = 2{,}735 \times x.$$

Therefore x or the concentration of carbon dioxid in the alveolar air would have been 4.74 per cent. had there been no excretion of carbon dioxid during the four second's interval.

The carbon dioxid excreted during the interval of four seconds was 27.8 c.c. which is 1.01 per cent. of the amount of air in the alveolae at the end of inspiration. This amount was 2,735 c.c.

If this be added to the supposed percentage of 4.74 per cent. we have 5.75 per cent., which is within 0.05 per cent. of the result obtained, namely, 5.80 per cent. This result was obtained with an inspiration of 875 c.c. What is the dilution when larger amounts are inspired?

G. expired one second, alveolar air = 6.23 per cent. carbon dioxid; inspired three seconds, then expired two seconds. Result:

Total expired air equals.....2,810 c.c.
Carbon dioxid in expired air equals 4.12 per cent.
Alveolar air equals.....5.09 per cent. CO_2
Total alveolar air equals.....2,274 c.c.
Dead space equals.....536 c.c.

We will not occupy space here to discuss the problem of the dead space, as that will be treated in a publication elsewhere. It will suffice for the present to say that the dead space is not enlarged, so we will retain the dead space as 140 c.c. Assuming the maximum excretion of 35.8 c.c. of carbon dioxid to have been the amount excreted during the interim of five seconds, we should have had a carbon dioxid content of 3.61 per cent. instead of 5.09 per cent., as we really found. The larger the inspiration in a normal lung the less effective (proportionately) the ventilation becomes; that is, the less effective (proportionately) is the carbon dioxid of the residual air diluted.

Therefore, the same minute volume of ventilating air will be less effective in an emphysematous lung, not merely because there is a larger amount of residual air to be diluted, but also because the diffusion of carbon dioxid is less effective in an enlarged infundibular space.

One supposes that in lung ventilation there is a sharp definition histologically and functionally between the dead-space air and the alveolar air which is in contact with the respiratory membrane. We would also suppose that the alveolar air (or air which is in contact with the respiratory membrane) being divided among several million chambers would have a uniform carbon dioxid content within a second's time after a maximum inspiratory effort. This is, however, not the case as we believe we have shown in several ways.

This diminishing effectiveness of ventilation in overdistended lungs is responsible for the apparent increase of the dead space in forced breathing while at rest and during exercise. It is a large factor in the limitations of endurance in physical exercise. It also is a large factor in the failure to reduce the carbon dioxid concentration of alveolar air in emphysema and asthma when the minute volume of air is mathematically adequate for the purpose.

The increased amount of residual air and enlargement of the alveolar spaces and bronchiolar narrowing will account for most of the symptoms in asthma, but there is often an inconsistency between cyanosis and the carbon dioxid percentage of the alveolar air.

As we have observed above, we can account for the increased carbon dioxid concentration in the alveolar air when there is little or no diminution in the minute volume of air, but there is another notable fact in asthma, namely, the very moderate increase in the percentage of carbon dioxid in the alveolar air when the patient is cyanotic.

Patient 1, Mrs. L., had cyanosis of the lips, finger-nails and ears during her attacks of asthma when the carbon dioxid of the alveolar air was not above 6 per cent.

R. J., the second patient, had on two occasions only a sufficiently high carbon dioxid content of his alveolar air to account for cyanosis. These days were August 30 and October 12, when the alveolar air had a carbon dioxid content of 7.6 per cent. and 8 per cent. These occasions are consistent enough. As we have found in emphysematous patients without asthma, the alveolar air must attain at least 7 per cent. carbon dioxid before the patient becomes cyanotic. Asthmatic patients have cyanosis with a carbon dioxid content of their alveolar air, which is not high enough to cause cyanosis in emphysema uncomplicated with asthma. How can this difference in the two conditions be explained? We cannot account for the difference in cyanosis in the two conditions on the basis of ventilatory function. It seems there must be an additional cause which requires an explanation. As was stated in the first pages of this discussion, we were unable to find any indications of an impairment in the minute volume of blood through the pulmonary circulation, but may there not be an increased content of blood in the respiratory vessels which could impair the function of external respiration, so we would then have the additional factor of impaired respiratory function added to the impaired ventilatory function?

The patient R. J. had an attack Aug. 30, 1913, which was attended with a distinct increase of carbon dioxid in the alveolar air. During the asthma the alveolar air carbon dioxid, in three specimens, was 7.1 per cent., 7.9 per cent. and 7.6 per cent. After epinephrin was given, three specimens contained 6.1 per cent., 5.7 per cent. and 6.2 per cent. of carbon dioxid.

After the attack the minute volume measured only 100 c.c. more than during the attack of asthma with cyanosis. This difference is of course negligible so far as ventilation of the lung is concerned. Increased residual air would not have been so large a factor because in this attack the evidences of bronchiolar stenosis were limited to the right lower lobe and the left upper lobe.

Bedside notes made at the time, describe the lower right lung border at the eighth, tenth and twelfth ribs, in the midclavicular, axillary and subcostal lines of the right side, and at symmetrical points on the left side, the lower lung border was at the sixth, eighth and tenth

ribs. The right costal border was drawn toward the median line during inspiration and the left costal border was drawn away from the median line during inspiration. The disparity in movement of the lower portions of the two lungs was so great that the notes describe the excursion of the thorax as presenting the appearance of inspiratory torsion of the lower thoracic regions. During the asthmatic attack the patient coughed up a lot of foamy blood-stained sputum. There were no signs of stasis in the heart, veins or liver, and the attack was completely relieved by a subcutaneous injection of 15 minims of 1:1,000 epinephrin.

It was this experience which first gave rise to the suspicion that hyperemia of the pulmonary vessels was a factor in the cyanosis of asthma.

Dec. 7, 1913, R. J. had another experience which was significant in this relation. He had an attack of asthma which seemed not unlike his former attacks. The signs of bronchiolar spasm were relieved by epinephrin, but he continued with his lamentations when the lung was no longer increased in volume sufficiently to cause inspiratory narrowing of the subcostal angle. There was no evidence of obstruction to inspiration. Expiration was much prolonged and the patient complained bitterly of great distress in the substernal region. In reply to our questions he said there was no pain, but he constantly complained of what he termed "a misery." There were no fine whistling râles in the lungs, but there was an abundance of coarse mucous and sonorous râles during inspiration and expiration.

The blood-pressure measured 175 systolic and 103 diastolic. Apomorphin $\frac{1}{20}$ grain was then given subcutaneously. This was followed directly by vomiting. The blood-pressure dropped to 123 systolic. The diastolic pressure could not be determined. The patient was perfectly comfortable and in about ten minutes he was sound asleep. This relief came after his distress had lasted many hours and repeated injections of morphin had failed to give any relief. Apomorphin was given on this occasion, not because it was believed there was any need of lowering the aortic pressure to relieve signs of incompetence of the left ventricle, but to procure the revulsant effect of dilatation of the splanchnic vessels.

The pathological physiology in this whole play of symptoms is not clear, but the whole course of the trouble looked very much as though hyperemia of the pulmonary vessels was the cause of the distress after bronchiolar spasm ceased.

In a former publication[3] it was suggested that an enlargement of the dead space may be partly responsible for the ineffective ventilation of

3. Hoover, C. F.: The Minute Volume and Alveolar Air in Pulmonary Emphysema, THE ARCHIVES INT. MED., 1913, xi, 52.

emphysematous lungs, but since then our further studies prove the dead space in emphysema is not enlarged. The increase of residual air and hyperdistention of the infundibula are the two causes for the high carbon dioxid content of alveolar air in emphysematous patients. Keith[4] (quoting Oppel's work) says, "If out of a rubber balloon a model of the terminal bronchiole and infundibulum and alveoli be made and inflated, it is the central or infundibular space which expands most, the alveoli implanted on its walls being widened, but at the same time rendered more shallow. The point which one seeks to emphasize is that it is not the alveoli but the infundibula that should be regarded as the essential expansile parts of the lung. The larger and more plentiful the infundibula in a part of the lung, the more readily will that part respond to any distending force." This anatomical conception is quite consistent with the results of our studies in lung ventilation, but when we consider that an infundibulum has a diameter of not more than 1 mm., and that in hyperdistention the infundibula of normal lungs cannot be enlarged more than 2 or 3 mm., it seems astonishing that when 2 liters of air distributed in such small chambers are diluted with the addition of 3.5 liters, the diffusion of gases are not uniform throughout the entire mass.

Such is, however, a fact and our failure to recognize this in the past has led to several false conceptions of ventilation of normal lungs and lungs affected with emphysema and asthma.

When G., a normal man, breathed tranquilly into a rubber bag for five minutes at the rate of 15 respirations per minute, the total expiration was 52,310 c.c.; the minute volume was 10,462 c.c.; each respiration was 697 c.c.

Two specimens of air taken from the total expired air contained 3.97 per cent. and 4.01 per cent. of carbon dioxid. His alveolar air contained 6.0 per cent.

Sam G., a patient who had severe emphysema without any signs of obstruction in his bronchial tree, breathed tranquilly at rest two minutes and breathed 45 times in the two minutes, the total expiration was 22,500 c.c.; the minute volume was 11,250 c.c.; each inspiration was 501 c.c.

The minute volume or expired air contained 4.74 per cent. and 4.61 per cent. carbon dioxid in two specimens.

Two specimens of the alveolar air, taken during the collection of the expired air, contained 7.17 per cent. and 7.44 per cent. carbon dioxid.

Sam G. had pronounced cyanosis, and although his minute volume of expired air was greater than that of G., Sam G. did not dilute the

4. Keith: In Further Advances in Physiology, Leonard Hill, p. 186.

carbon dioxid of his alveolar air nearly so well as did G. The dead space, however, as measured on the basis of the difference in carbon dioxid concentration in the alveolar and total expired air, showed the dead space in the two men to be practically the same. The dead space in both measured between 150 and 165 c.c. The dead spaces in the two men were measured a great many times when they were breathing tranquilly and we never found the dead space enlarged in the emphysematous man, nor did we find the dead space enlarged in two other emphysematous patients whose minute volume air and alveolar air were examined many times.

It was shown in a former publication[3] how an emphysematous patient was cyanotic on one occasion when his minute volume of air and respiratory rate were the same as on a subsequent occasion when his emphysema and cyanosis and carbon dioxid concentration in the alveolar air had all diminished. In other words, the minute volume and respiratory rate remaining the same, when emphysema appears the patient will be cyanotic and the alveolar air carbon dioxid percentage will be raised. It seems by exclusion and direct evidence we may say that the real difficulty of ventilation in emphysema and asthma lies in the distention of the infundibula, and this fails to allow an equal diffusion of carbon dioxid throughout the alveolar air.

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EFFECT OF INTRAVENOUS AND INTRASPINAL TREATMENTS ON CEREBROSPINAL SYPHILIS *

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With the demonstration by Noguchi[1] of *Spirochaeta pallida* in the central nervous system tissues, and with the successful use of salvarsan, paresis and locomotor ataxia have become less matters of purely neurological concern and more problems of infection, immunity and chemotherapy. Under this aspect the syphilitic disturbances of the central nervous system function have taken on a new interest alike for the student of immunity, the clinician and the psychologist. For it is now clear that the symptoms of central nervous system syphilis, be they pain, ataxia, or psychic disturbance, depend, as is the case in acute poliomyelitis, on the location of the damaging lesions.

The therapeutic problem, therefore, is fundamentally of a similar nature to that found in any infection in which the specific agent is sent to destroy the infecting organism. The agent and organism must be brought into contact. The well-known impermeability of the choroid plexus to foreign substances renders the access of parenterally given drugs to the brain and cord difficult; consequently, it is to be inferred that salvarsan, when it is introduced into the blood-stream, comes in very minute quantities, if at all, into contact with spirochetes, lying within the meninges or in the outer layers of the brain. It has been shown, however, that the choroid membranes can be rendered more passable by injury or inflammation. Furthermore, Flexner[2] has demonstrated that immune serum may be introduced most effectually in certain bacterial infections of the meninges. Purposing to bring the largest possible amount of salvarsan in contact with the brain and cord, numerous workers have employed each or both of the principles just mentioned. Sicard has argued most urgently that in the damaging effect of the spinal injections lies their real importance. To accomplish this end he has injected 5 c.c. of a 0.5 per cent. sodium chlorid solution intracortically through a small trephined opening in the skull. Twenty-four hours later he has given an intravenous injection of salvarsan. Robertson[3] in Edinburgh was perhaps the first to

* Submitted for publication, July 7, 1914.

1. Noguchi and Moore: Jour. Exper. Med., 1913, xvii, 232.

2. Flexner and Jobling: An Analysis of Four Hundred Cases of Epidemic Meningitis Treated with the Antimeningitis Serum, Jour. Am. Med. Assn., 1908, li, 269.

3. Robertson: Edinburgh Med. Jour., 1913, x, 428.

use salvarsanated serum by intraspinal injection, but his cases were not followed over a definite period of time and the reports are not complete.

During the past year a considerable amount of work has been done by the French, especially Marinesco,[4] Levaditi,[5] Marie,[6] Jeanselme, Vernes, Bloch,[7] Ravaut,[8] Sicard and Riley. These workers, as well as Wechselmann,[10] in Germany, have given intraspinal injections of neosalvarsan in solution. Some have used as high as 10 or 12 mg. at a dose. None of the cases have been followed over a sufficient period of time, however, and the reports are very incomplete. In almost all of the cases there were serious symptoms of an undesirable nature, the most prominent of these being retention of urine. Many of the patients also had convulsive attacks following injection. Most of the work was done on patients suffering from general paresis. In general it may be said that the reports of all these observers are limited in detail and the results did not seem to warrant the rather severe symptoms which many have reported. The scope of this paper does not permit a report of the work of the various authors but a full bibliography is given in the footnotes. By far the most careful work on the subject of treatment of syphilis of the central nervous system by intraspinal injection is that of Swift and Ellis.[11] These authors report a series of twenty cases which have been followed for a year or more with improvement in symptoms and serological findings resulting from treatment.

The present work may be considered as merely a continuation of their series, for, with certain minor modifications necessitated by circumstances arising outside of institutional control, the technic and methods of management are those described by them.

Twenty-five cases have been selected for presentation. Symptomatically they have been arranged so that pain predominates at one end of the series and psychic disturbance at the other. Cytologically and serologically they cannot be classified profitably. These two factors

4. Marinesco: Ztschr. f. diätet. u. physik. Therap., 1913, xvii, 194; Marinesco and Minea: Bull. de l'Acad. de méd., 1914, lxxvi, 259.

5. Marie and Levaditi: Bull. et mém. Soc. d. Hôp., 1913, xxix, 675.

6. Levaditi, Marie and Martel: Soc. de Biol., 1913, lxxv, 567.

7. Jeanselme, E., Vernes, A., and Bloch, M.: Du traitement des femmes syphilitiques enceintes par le salvarsan, Bull. et. mém. Soc. d. Hôp., 1913, xxix, 792.

8. Ravault: Bull. et mém. Soc. d. Hôp., 1913, xxix, 752.

9. Sicard and Reilly: Bull. et. mém. Soc. d. Hôp., 1913, xxix, 861.

10. Wechselmann: Deutsch. med. Wchnschr., 1912, xxxviii, 1446.

11. Swift, Homer F., and Ellis, Arthur W. M.: The Treatment of Syphilitic Affections of the Central Nervous System with Especial Reference to the Use of Intraspinous Injections, THE ARCHIVES INT. MED., 1913, xii, 331.

led to the expression of the analogy to poliomyelitis, namely, that it is not the nature of the infection so much as the location that determines the symptoms in central nervous syphilis. These twenty-five patients were all treated intensively for active syphilis. All but one received combined intravenous and intraspinal injections. Mercury and potassium iodid were also used, but the chief reliance and interest were centered on the action of salvarsan, neosalvarsan and salvarsanated serum.

Intravenously most of the patients were treated at weekly intervals with doses of salvarsan varying from 0.3 to 0.6 gm., or neosalvarsan in full doses. Salvarsan was the drug of choice and was changed for neosalvarsan only when the patient had an anaphylactic reaction. The usual technic in the preparation of doses was observed. Intraspinally most of the cases received 30 c.c. of 50 per cent., or from 20 to 25 c.c. of full-strength serum, separated by centrifugalization from blood withdrawn forty minutes after the intravenous dose of salvarsan. The serum was heated to 56 C. and was introduced intraspinally the same day. Lately several patients have been bled before the intravenous dose, and then salvarsan up to a milligram added in vitro to the serum. This mixture was heated to 37.5 C. for forty minutes, and then 56 C. for half an hour. No serious symptoms followed any of the injections. Some patients had increase of pain for a few hours following the injection. This, however, could usually be controlled by phenacetin, caffein and codein. Occasionally morphin was used. Once spinal fluid was removed by puncture fourteen hours after treatment to relieve the pain. Recently, however, there has appeared in several cases a subjective feeling of numbness of the feet and legs, usually below the knee, but in some cases reaching to the hips and involving the perineum. Cutaneous sensation is not impaired. The symptom has occurred with one exception in patients who received serum salvarsanated in vitro. It seems probable, however, that there is a definite association between treatment with this form of serum and the symptom of numbness. The patients have noticed no discomfort at the time of treatment and have first complained of the numb feeling after three or four injections have been given. Not all patients who have received directly salvarsanized serum have shown the symptom, and none have had the bladder disturbance described by those who have injected salvarsan into the dural sac. In a recent publication Gennerich[12] has noted symptoms not unlike those which have been described here in patients to whom he has given neosalvarsan intraspinally.

12. Gennerich: München. med. Wchnschr., 1914, lxi, 823.

Another unsatisfactory event which is unassociated apparently with serum directly salvarsanized, but which has been seen in patients treated by both methods, is the sudden increase of ataxia following a period of definite improvement. If all treatment is stopped in these cases and rest with massage and increasing educational exercises is instituted the ataxia improves fairly rapidly. This phenomenon is especially striking in Case 96; for after the spinal fluid findings had returned to normal and the patient felt extremely well and encouraged, there was a sudden onset of ataxia, worse than any he had previously experienced. Case 76 behaved in a similar manner.

The cases have been grouped according to symptoms and not according to their spinal fluid findings, because it was found that spinal fluid changes varied very greatly in all the groups, and no classification was possible.

GROUP I: CASES WITH PAIN

The first group of cases is composed of those individuals who complained of pain. Three of them had no ataxia; one had a very slight Romberg sign. Their physical signs were typical of the condition known as locomotor ataxia, as regards pupils, reflexes and sensory disturbances, with the exception of one woman whose knee-jerks were exaggerated.

CASE 49.—W. A. F., man, aged 45; chancre twelve years ago; no secondaries; very small amount of treatment; perfectly well until 1912 (two years ago); then numbness of great toe followed by slight unsteadiness, giving trouble in running or walking; shooting pains in the testicles; girdle sensation; shooting pains in the legs.

Physical Examination.—Pupils a little sluggish; knee-jerks and Achilles jerks absent; Romberg sign present.

Spinal Fluid.—Clear, pressure normal; 25 cells; globulin ±, Wassermann negative throughout. Patient was given a series of intravenous injections of salvarsan, no intraspinous; marked improvement.

CASE 17.—J. L., woman, aged 56; doubtful miscarriage; two children; no knowledge of infection; no secondaries; tremendous pain in arm and fingers; less in legs and toes.

Physical Examination.—Pupils unequal, small, irregular, Argyll Robertson; reflexes upper and lower all exaggerated; sensation, pain slightly diminished.

Spinal Fluid.—Clear, pressure low; cells 37; globulin +++; Wassermann +++ in 0.3 c.c.; patient treated intensively by intravenous and intraspinal injection; at the end of four months pains much less.

Spinal Fluid.—Clear; pressure low; cells 5; globulin-Wassermann ++ in 0.5 c.c.

CASE 126.—Dr. L., aged 48. Suffering abdominal pain for the past two or three years; occasional pains in legs. No knowledge of infection; no secondaries.

Physical Examination.—Pupils small, equal; Argyll Robertson; knee-jerks and Achilles jerks absent; sensation, diminution of pain sense over the lower legs.

Spinal Fluid.—Clear, pressure increased; cells 52; globulin +; Wassermann +++ in 0.1 c.c.; blood-serum ++. At the end of four months marked improvement in symptoms. No change in physical signs. Spinal fluid clear, pressure slightly increased; cells 0; globulin ++; Wassermann +++ in 0.5 c.c. Blood-serum negative; severe dermatitis; treatment suspended.

CASE 76.—J. P. L., man, aged 32, chancre seven years ago; well treated; mercury; no secondaries; for the last five or six years pains in legs; increasing ataxia.

Physical Examination.—Pupils small, Argyll Robertson; reflexes, knee-jerks and Achilles jerks absent; sensation, scattered areas of loss of touch and pain; Romberg sign moderately marked.

Spinal Fluid.—Clear, pressure normal; cells 40; globulin +; Wassermann ± in 0.3 c.c., +++ in 0.5 c.c. Blood serum +++. Patient given intensive treatment for three months at which time symptoms somewhat improved.

Spinal Fluid.—Twenty-two cells; globulin ±; Wassermann +++ in 0.5 c.c. Intraspinal treatment begun. Spinal fluid, after three treatments, 5 cells; globulin +; Wassermann + in 0.5 c.c.; blood-serum ++; sudden increase of ataxia.

GROUP II: CASES WITH PAIN AND ATAXIA

The second group of cases comprises text-book examples of locomotor ataxia, cases in which pain, ataxia and physical signs are well marked.

CASE 103.—S. H. P., man, aged 37; chancre (?) treatment (?). Patient had great pain in legs and very marked ataxia.

Physical Examination.—Pupils irregular; react slightly to light and accommodation; knee-jerks and Achilles jerks absent; areas of analgesia about abdomen, back and feet.

Spinal Fluid.—Cells 110; globulin ++; Wassermann + in 0.5 c.c. Patient received a series of four injections of neosalvarsan, followed by a long series of mercury for two months, at the end of which time spinal fluid had 7 cells; moderate globulin; Wassermann negative. He then received six more injections of salvarsan, followed by another series of mercury. He went away for the summer. Three months later spinal fluid showed 41 cells; globulin ±; Wassermann + in 0.5 c.c. He was treated again intravenously and given two intraspinal treatments. These caused very great pain and were discontinued. Patient given intravenous treatment five times, at the end of which time spinal fluid had 8 cells; globulin normal; Wassermann negative. No further treatment for two months. Puncture done again, showed 8 cells; globulin ±, Wassermann doubtful in 0.5 c.c. This case suggests very strongly that the intravenous treatment alone was insufficient.

CASE 128.—O. T. S., man, aged 53. Chancre thirty years ago; mild secondaries; well treated with mercury; pains began ten years ago; has had one intramuscular and three intravenous injections of salvarsan.

Physical Examination.—Ptosis of left lid; pupils Argyll Robertson; slight pallor of disk; knee-jerks and Achilles jerks absent; sensation disturbed.

Spinal Fluid.—Faintly blood-tinged; pressure increased; 22 cells; globulin +; Wassermann ++ in 0.3 c.c.; blood-serum + in 0.2 c.c. Duration of treatment five and one-half months; sixteen intravenous and six intraspinal injections; the latter always caused pain. Patient improved after the first three, then began to go down hill; became melancholic, considerably depleted; terminal bronchopneumonia.

CASE 93.—J. S., aged 42, no chancre, no secondaries; gonorrhea two or three times; three years ago numbness in the feet; six months ago trouble in walking; has improved since; has had two doses of salvarsan and mercury rubs.

Physical Examination.—Pupils pin-point, do not react; knee-jerks absent; sensation disturbed, chiefly hyperesthesia; Romberg marked.

Spinal Fluid.—Three hundred and seventy-five cells; globulin +; Wassermann +++ in 0.1 c.c. Patient had treatment for twelve months with some intermissions; improved considerably.

Spinal Fluid.—Pressure normal; cells 20; globulin +; Wassermann + in 0.5 c.c. Physical signs not changed; pain following intraspinal treatment.

CASE 94.—T. W. S., man, aged 34. Chancre fifteen years ago, no treatment; pain, ataxia, loss of weight.

Physical Examination.—Pupils Argyll Robertson, mid-wide, knee-jerks and ankle-jerks absent; sensation touch and pain gone over the feet and legs; marked ataxia.

Spinal Fluid.—Clear, pressure low, cells 131. globulin +; Wassermann ++ in 0.3 c.c. Patient under treatment for ten and a half months; nineteen intravenous and three intraspinal injections. The latter always caused pain; once puncture had to be done fourteen hours after treatment to relieve pain. Very marked improvement; patient gained weight. Spinal fluid pressure normal; 5 cells; globulin ±; Wassermann negative.

CASE 21.—J. M. D., man, aged 54. Chancre twenty-nine years ago; slight secondaries; disappeared rapidly; well ever since; five years ago pains; marked ataxia; morphinism.

Physical Examination.—Pupils small; Argyll Robertson present; knee-jerks and Achilles jerks absent; sensation, pain lost below level of nipples; marked Romberg sign.

Spinal Fluid.—Clear, pressure increased; cells 62; globulin ++; Wassermann negative. Patient given six injections of salvarsan, one intraspinal. Spinal fluid: cells 21; globulin ++; Wassermann negative; very severe pain following last treatment; took 4 grains of morphin during the night; has not reappeared.

CASE 89.—M. D., man, aged 46. Gonorrhea eighteen years ago; two months later rash; treated with inunctions for three weeks, since then nothing. Seven years ago began to have pains which have persisted ever since; ataxia.

Physical Examination.—Pupils unequal, one Argyll Robertson, the other reacts slightly to light. Knee-jerks and Achilles jerks absent; also biceps and triceps.

Spinal Fluid.—Clear, pressure low; cells 66; globulin +; Wassermann ++ in 0.3 c.c. Patient has been under treatment one and one-half months; has had seven intravenous and four intraspinal injections; pain becoming less. Spinal fluid: cells 8; clear; pressure low; globulin +; Wassermann +++ in 0.5 c.c. Patient is a moderate morphinist.

GROUP III: ATAXIA WITHOUT PAIN

The third group is made up of those patients who have a simple ataxia and no pain. The physical signs of these cases were also almost typical.

CASE 95.—W. S. P., man, aged 47. Gonorrhea twenty-three years ago, no chancre, no secondaries; seven years ago had an ulcer on the leg, the result of injury, but it was said subsequently to be syphilitic. Four months ago patient fell and struck his head; unconscious for four hours; three weeks later noticed

weakness in legs, lack of control, no pain; recently slight circular pain about the waist; slight emotional disturbance; instability.

Physical Examination.—Pupils equal; react to light; sensation, pharynx anesthetic, diminution of touch and pain over the arm and round right elbow, and over heart-shaped area over end of spine.

Spinal Fluid.—Clear, pressure not increased; cells 51; globulin +; Wassermann ++ in 0.5 c.c. Patient given several injections of mercury before salvarsan was started; has been under treatment four and one-half months; sixteen intravenous injections, at the end of which time spinal fluid had 5 cells; globulin ± to +; Wassermann + in 0.5 c.c. Since then he has been given two intraspinal injections. Spinal fluid clear; pressure normal; cells 10; globulin ±; Wassermann + to ++ in 0.5 c.c. Patient is very much steadier, is able to work all day and feels a great deal better.

CASE 96.—W. A. F., man, aged, 36. Father died of paresis. Seven years ago soft chancre; no treatment; no secondaries; two years ago became talkative; since then nothing; past two or three months unsteadiness in walking.

Physical Examination.—Pupils equal, regular, Argyll Robertson; knee-jerks and Achilles jerks absent; sensation normal. Romberg sign; very slight general tremulousness; seems to be very slightly dull mentally.

Spinal Fluid.—Clear; pressure slightly increased; cells 133; Wassermann +++ in 0.3 c.c.; blood-serum +++. Patient started with mercury; then given ten intravenous and five intraspinal injections. Patient remarkably improved; mental dulness disappeared; ataxia still marked. Spinal fluid: clear; pressure normal; cells 6; globulin ++; Wassermann — in 0.5 c.c.

CASE 124.—P. S. P., man, aged 36. Soft chancre eleven years ago, no secondaries; no treatment; ten months ago unsteadiness in feet, increasing; at present extreme ataxia, very little pain.

Physical Examination.—Pupils Argyll Robertson, Romberg marked.

Spinal Fluid.—Clear, cells 11; pressure normal; globulin +; Wassermann ++ in 0.1 c.c. Patient has had six injections of salvarsan and four intraspinal treatments. No change yet in symptoms, except perhaps increase in ataxia.

Spinal Fluid.—Clear, cells 11; pressure normal; globulin +; Wassermann +++ in 0.5 c.c.

GROUP IV: CASES WITH OPTIC ATROPHY

The fourth group consists of those most distressing cases of failing vision, due to optic atrophy. The strange thing about them is that, notwithstanding extreme changes in spinal fluids and other evidences of syphilitic disease of the central nervous system, the patients have been absolutely unconscious of anything amiss except increasing blindness. Some forms of syphilitic meningitis indeed seem to be compatible with years of comparative health. In cerebrospinal syphilis the spinal fluids with increased cells and heavy globulin content indicate inflammation of the meninges. Optic atrophy in these cases is due, according to Stargardt[13] to the pressure of exudates on the nerves. According to this view, then, the final state of vision following treatment depends on whether or not pressure can be removed before nerve atrophy has set in. From the patients' point of view these

13. Stargardt: Arch. f. Psych. u. Nervenkr., 1913, li, 711.

cases have been disappointing except in one very early case. From the point of view of effect on the infection of the central nervous system, as shown by the spinal fluid changes, treatment is fairly satisfactory.

CASE 91.—J. N. W., man, aged 40 years. Gonorrhea twenty years ago, again three years ago; no knowledge of chancre, no secondaries; double vision ten years ago; three years ago Argyll Robertson pupil discovered accidentally; Wassermann negative, no treatment. One year ago again eye change was accidentally discovered and the patient was immediately put on mercury; has been having mercury off and on ever since. Patient experiences no discomfort of any kind, except that he is intensely nervous and energetic.

Physical Examination.—Pupils unequal, reaction to light absent, except perhaps a very slight movement in the right pupil; disks show distinct pallor and visual fields slightly contracted, especially color-field. Knee-jerks present and active. Sensation not disturbed.

Spinal Fluid.—Clear; pressure normal; cells 53; globulin +; Wassermann ± in 0.3 c.c., ± to + in 0.5 c.c. Patient given nine injections intravenously; also four or five injections of mercury over a period of five months, at the end of which time patient seems in splendid health; disks appear normal; color-fields stationary but show improvement over the original examination. Spinal fluid: clear, pressure normal, cells 15; globulin ± to +. Wassermann negative throughout.

CASE 90.—C. P., woman, aged 34, married ten years. (Husband has been under treatment for cerebrospinal syphilis.) Patient unaware of any infection; two months ago began to notice that her eyes were less good; no trouble in the dark, but bright light dazzled her; absolutely no symptoms.

Physical Examination.—Pupils react normally, possibly a trifle sluggishly; disks wide; small vessels, narrow; fields markedly contracted; knee-jerks present; right diminished; left active; Achilles jerks present; sensation, heart-shaped area at end of spine diminished to pain.

Spinal Fluid.—Clear, pressure normal; cells 120; globulin +; Wassermann + + + in 0.3 c.c. Blood-serum + + +. Patient given intensive treatment with mercury and salvarsan; during seven and one-half months nineteen intravenous and eleven intraspinal injections. There is practically no change in vision. In general health patient feels much better; for the last three or four weeks has had a sensation of numbness; hypersensitive below the knees. Spinal fluid: clear, pressure normal, cells 3, globulin ±, Wassermann + in 0.5 c.c.; blood-serum negative.

CASE 26.—O. B. P., man, aged 41, chancre twenty years ago; slight secondaries; no trouble until two years ago, when he noticed blurred vision; has had shooting pains for ten or twelve years down the front of his shins; put on mercury; patient now very nearly blind.

Physical Examination.—Pupils mid-wide; react very slightly to light; disks white with bluish tinge; vessels very small and thread-like; reflexes, knee-jerks active; Achilles jerk active.

Spinal Fluid.—Clear, pressure slightly increased; cells 133; globulin ++; Wassermann 0.05 c.c. ++; blood-serum ++. Patient treated intensively for four months; fourteen intravenous injections; six intraspinal; after first two or three weeks patient noticed definite growing worse of the vision; recently, however, it has returned to what it was before treatment began. Spinal fluid: clear, pressure normal, cells 8, globulin +; Wassermann 0.1 +. This patient treated entirely with serum salvarsanated *in vitro*.

CASE 44.—E. S., man, aged 52. Chancre twenty-five years ago; very little treatment; slight secondaries; two and one-half years ago double vision; eight

Symptoms	Patient	Case	Pressure	Cells	Globulin	W. R. Spinal Fluid	W. R. Blood	Clinical Complaint	Physical Examination	Duration of Treatment
Pain.....	W. A. F.	49	Normal	25	±	0.5 —	—	Pain 2 years., numbness, girdle sensation	Pupils sluggish; K. J. —	9
	J. L.	17	Low	37	++	0.2 +++	Not done	8 years pain in arms	A. R. pupils; K.J. ++; sensation disturbed	5
	Dr. L. ..	126	+	52	+	0.1 +++	++	10 years gastric crises, nervousness	A. R. pupils; K. J. —; sensation disturbed	4
	J. P. L.	76	Normal	40	+	0.2 ±	+++	8 years pain, weakness, sl. ataxia	A. R. pupils; K. J. —; rapid heart	5
Pain and Ataxia...	S. H. P.	103	Normal	110	++	0.5 +	—	Pain, ataxia	A. R. pupils; K. J. —; sensation disturbed	11
	S. H. P.	103	Normal	52	—	0.5 ++	—	.....	Pupils unequal; react to light slow	6
	O. T. S.	128	++	22	+	0.3 ++	+	Pain 10 years, ataxia	A. R. pupils; K. J. —; sensation disturbed	5.5
	J. S.	93	+	375	+	0.1 +++	Not done	Pain, ataxia 3 years	A. R. pupils; K. J. —; sensation disturbed	12
	J. W. S.	94	Low	131	+	0.3 ++	+++	Pain, ataxia 5 years	A. R. pupils; K. J. —; sensation disturbed	10.5
	J. M. D.	21	++	62	++	0.5 —	+++	Pain, ataxia morphin	A. R. pupils; K. J. —; sensation disturbed	2
	M. D. ...	89	Low	66	+	0.3 ++	—	Pain 7 years, ataxia, morphin	A. R. pupils; K. J. —	3.5
Ataxia...	W. S. P.	95	Normal	51	+	0.5 ++	Not done	Pain 4 months, slight ataxia, irritability	Pupils very sluggish; K. J. —; sensation disturbed	7
	W. A. F.	96	+	133	+++	0.2 +++	+++	Ataxaia 2 to 3 months	Pupils equal, regular; react to light and accom.; K. J. —	3
	P. S. P.	124	Normal	62	++	0.1 +++	+++	Ataxia 7 mos.	A. R. pupils; K. J. —	2.5
Optic Atrophy	J. N. W.	91	Normal	58	+	0.2 ± 0.5 ± to +	—	None	A. R. pupils; contracted fields; pupils not equal	6.5
	C. P. ...	90	Normal	120	+	0.2 +++	+++	2 months failing vision	Pupils sluggish; fields narrow; sensation disturbed	7.5
	O. B. P.	26	+	133	++	0.5 ++	+++	2 years failing vision	Pupils sluggish; K. J. present; A. J. active	4
	E. S.	44	Normal	75	+	0.1 ++	++	2.5 yrs. almost blind, ataxia	Fixed pupils; aortitis; K. J. —	2.5
Bulbar...	H. V. D.	22	+	52	+++	0.2 ++	++	Cyclic vomiting, vagotonia 8 years	Pupils sluggish; heart slow; K J. +; sensation disturbed	9
Psychic Disturbance....	L. B. K.	18	++	40	++	0.1 +++	+++	Depression, vague fears 3 months	A. R. pupils, not equal K. J. sluggish; sensation disturbed	4
	A. S. B.	12	Normal	25	+	0.1 +++	+++	Mentally sluggish; speech thick and hesitating 1 year	Pupils o. k.; grip not equal; K. J. ++	6.5
	C. R. C.	25	++	327	+++	0.5 +++	+++	Nervousness, vomiting, dizziness 2 weeks	Pupils not equal; reaction slow and stiff; K. J. —	9
	R. F. ...	129	Low	27	++	0.1 +	+	Dulness, depression, wandering 6 years	Pupils nearly equal; reaction to light slow; tremor; K. J. ++	2.5
	F. S. C.	24	+	5	±	0.2 +++	—	Dulness, loss of insight; hemiplegia, 8 years	Pupils pin point and A. R.; right, K. J. —; left, K. J. ++	9
	H. H. S.	102	+	24	+	0.1 ++	++	Dulness, wandering speech 6 mos., typical 3 weeks	A. R. pupils; K. J. —; tremor	14
	J. C. H.	66	+	70	±	0.1 ++	0.1± 0.2++	Expansion, excitability, delusions 1 wk.	Pupils small, irreg., fixed; K.J. —; tremor	10

* Fluid had been negative, this after three months without treatment.

—Treatments on Cerebrospinal Syphilis

No. Intravenous	No. Intraspinous	Pressure	Cells	Globulin	W. R. Spinal Fluid	W. R. Blood	Clinical Complaint	Physical Signs	Time Without Symptoms
10	0	Normal	1	− to ±	0.5 −	−	Marked improvement	.....	Nine months.
14	9	Low	5	+ to ++	0.5 ++	++	Marked improvement	K. J. less active, no other change.	
9	5	Sl. +	0	++	0.5 +++	−	Marked improvement	No change.....	Severe As. dermatitis.
17	5	....	1.2	± to +	0.5 + to ++	++	Improved	No change.....	Sudden increase in ataxia.
10	0	Normal	52*	−	0.5 ++	−	Great improvement...	Pupils react to lt. and accom.	Two months.
23	2	Normal	8	− to ±	0.5 −	−	Great improvement...	Pupils react; K. J. −	Two months.
16	6	Normal	...	+	0.3 ++	−	Decline, death.....	No change.	
23	8	Normal	2	+	0.5 ++	....	Considerable improvement	No change.	
19	3	Low	3	± to +	0.5 −	....	Marked improvement	No change.	
5	2	+	21	++	Not done	Not done	Very severe pain.....	No change.....	Pt. disappeared.
13	6	Low	8	.....	0.5 ++ to +++	....	Marked improvement	No change.	
21	3	Normal	10	++	0.3 ± 0.5 +++	−	Slight improvement...	No change.	
10	5	Normal	6	++	−	....	Marked improvement	No change.....	Sudden onset of ataxia.
6	4	....	11	+	0.5 +++	....	Considerable improvement	No change.	
10	0	....	15	± to +	−	....	Marked improvement in fields.		
19	11	Normal	3	±	0.5 +	−	General condition improved	Fields narrowing; vision less.	
14	6	Normal	8	+	0.1 + 0.3 +++ 0.5 +++	....	Stationary, pain started	No change.....	Slight numbness in calves.
6	7	Normal	13	± to +	0.3 ++	....	No change.....	No change.	
24	12	Normal	10	.....	0.5 ±	−	Entirely well.....	Practically clear	4 to 5 months without symptoms.
11	9	Normal	23	.....	++	0.5++	Marked improvement	No change.	
21	11	Normal	8	+	0.5 +	....	All clear.....	Reflexes sl. +...	Slight numbness in feet.
22	15	Normal	33	++	0.3 +++	+++	Apparently clear.....	Pupils react more promptly	Numbness in feet
6	5	Normal	32	+++	0.3 + 0.5 +++	....	Marked improvement	No change.	
36	18	Low	2	+	0.5 +	−	Mentally active; insight poor; hemiplegia better	No change.	
20	9	+	18	+	0.3 + 0.5 +++	0.2++	Entirely clear; at work	Pupils react to light; no other change.	
16	8	Normal	5	Omitted	0.5 ±	+++	Entirely clear.....	No change.	

months ago eyes began to fail; had had four injections of salvarsan; ten injections of mercury; aside from failing vision patient feels well; somewhat unsteady.

Physical Examination.—Pupils wide, fixed, irregular, disks bluish white; oval; vessels small, thread-like; patient apparently absolutely blind, although he can distinguish light from dark; dilatation of aorta, double aortic murmur. Blood-pressure, 210; pulse 100 to 140; reflexes, knee-jerks and Achilles jerks absent.

Spinal Fluid.—Seventy-five cells; globulin +; Wassermann ++ in 0.1 c.c. Patient given six intravenous and seven intraspinal injections. Spinal fluid: then clear; pressure normal; cells 13; globulin ± to +; Wassermann in 0.3 c.c. ++; no change in vision or in any other physical signs.

GROUP V: CASE OF VAGUS INVOLVEMENT

The fifth group comprises only one case, which it was thought wise to class by itself because of the striking symptom-complex, depending on the involvement of a single bulbar nerve, the vagus. A startling picture of vagus hypertonia was found; this cleared up temporarily following atropin paralysis of the nerve. It was permanently cured after combined intravenous and intraspinal treatment.

CASE 22.—H. V. D., man, aged 40 years. Severe cyclic vomiting, associated with slow pulse, sinus arhythmia, sweating and prostration; chancre fourteen years ago; pill treatment; secondaries; stomach trouble in 1906; diplopia on two or three occasions.

Physical Examination.—Pupils unequal, irregular, reaction to light stiff; knee-jerks and Achilles jerks very active; sensation, scattered disturbance in touch and pain sensation.

Spinal Fluid.—Fifty-two cells; globulin ++; Wassermann ++ in 0.3 c.c. Patient under treatment for nine months; twenty-four intravenous and twelve intraspinal injections. Patient has been absolutely without symptoms for the past three months. Spinal fluid: clear, pressure normal, cells 10, globulin +, Wassermann ± in 0.5 c.c.

GROUP VI: CASES WITH PSYCHIC DISTURBANCE

The sixth and last group of cases contains instances of psychic disturbance. These varied from confusion, depression and irritability, to expansive ideas, delusions and mania. These cases show remarkable improvement in symptoms, but very slight, if any, improvement in physical signs. There were two types of response in the spinal fluid: the first in which the fluid returned to normal very promptly; the second in which the cell-count came down slowly and the Wassermann rarely disappeared in 0.3 c. c. Clinically, however, no matter what the spinal fluid showed, the cases improved promptly.

CASE 18.—L. M. K., man, aged 42. Chancre twenty years ago; typical secondaries; treated with mercury four or five years; since then perfectly well; three months ago general failure of health, loss of cheerfulness; became nervous and depressed; no headache; no dizzy spells.

Physical Examination.—Patient slow in discourse; sometimes loses thread of thought; pupils unequal, irregular, Argyll Robertson; faint tremor of tongue and lips; knee-jerks sluggish; sensation, scattered loss of pain and touch over lower extremities.

Spinal Fluid.—Clear; pressure increased; cells 40; globulin ++; Wassermann +++ in 0.1 c.c.; patient treated for four months; received eleven intravenous and nine intraspinal injections. Patient has been treated with serum from another case. He has developed a general dry, itching dermatitis and outcrop of small, slate-colored, pigmented spots from 1 mg. to 2 mg. in diameter; on account of this finding salvarsan has been discontinued. There has been a marked improvement in the patient's symptoms, but he looks bad, pasty and yellow. Spinal fluid: 23 cells, globulin ±, Wassermann ++ in 0.5 c.c.

CASE 12.—A. S. B., man, aged 36. Chancre twelve years ago; well treated with mercury; treated almost constantly ever since; nine months ago fell on his head while hunting; though not unconscious was unable to speak; was thought to have a fracture of the base; definite slowness in speech and mental activity.

Physical Examination.—Pupils equal and react normally; tendon reflexes very much exaggerated, almost clonus; sensation, diminished pain sense over all, especially lower extremities; memory inaccurate; writing very slow and difficult with a good many mistakes; speech slow, hesitating.

Spinal Fluid.—Clear; pressure normal; cells 24; globulin +; Wassermann +++ in 0.1 c.c.; blood-serum +++. Patient under treatment six and one-half months; has had twenty-one intravenous and eleven intraspinal injections. After the first intravenous injection patient vomited, projectile type; pulse-rate was 66. Since then symptoms have cleared up entirely. Knee-jerks diminished, but now speech is practically without hitch; writes as well as ever. Spinal fluid: clear, pressure normal, cells 8, globulin ± to +; Wassermann + in 0.5 c.c.

CASE 25.—C. R. C., man, aged 55. Chancre many years ago; treated five years with mercury, never taken well; no signs until a year ago when he had sore mouth; mercury again for six months. Two weeks ago patient fell and struck the back of his head; he was not unconscious; vomited; has been in poor health since; has occasional dizziness, nausea and rapid pulse; marked psychic restlessness.

Physical Examination.—Pupils unequal, reaction to light slow and stiff; knee-jerks absent; hearing of left ear slightly impaired; patient has been inclined to be garrulous at times during the past year; sensation not changed.

Spinal Fluid.—Clear, pressure increased, cells 327; globulin +++; Wassermann +++ in 0.05 c.c.; blood-serum +++. Patient has been under treatment nine months; twenty-two intravenous and fifteen intraspinal injections; clinically he is apparently well. Spinal fluid: clear, pressure normal, cells 33, globulin ++; Wassermann +++ in 0.3 c.c. Serological reactions in this case have been extremely stubborn; they have apparently no relation to symptomatology, which has cleared up entirely, save for numbness of feet.

CASE 24.—Dr. F. S. C., man, aged 47. Specific infection at operation eighteen years ago. Eight years ago had a sudden noise in the right ear followed by nausea and vomiting; had slight attack previously; improved after some months and went back to work, but never really normal; three years ago Wassermann +++; given salvarsan several times; during that year weak, with dizziness and vomiting; numbness of left side; complete left hemiplegia and speech disturbance; again given salvarsan; greatly improved; since then had been very depressed; sluggish thought.

Physical Examination.—Patient has a rather idiotic expression; speech slow, hesitating; pupils pin-point; Argyll Robertson; remains of hemiplegia noted, including left angle of mouth; weakness of left arm and leg; knee-jerks, left

active; right absent; sensation, no disturbance made out; there is a distinct disturbance of equilibrium.

Spinal Fluid.—Five cells; globulin ±; Wassermann +++ in 0.5 c.c. Blood-serum negative. Patient has been under treatment for nine months; thirty-six intravenous and eighteen intraspinal injections. He has improved markedly clinically but still shows definite mental symptoms of the paretic type. He is able to write on the typewriter and walk; is learning to try and help himself. In this respect there has been a very marked change of personality. Spinal fluid shows 2 cells, clear, low pressure, globulin +, Wassermann + in 0.5 c.c.; blood-serum negative.

CASE 112.—H. H. S., man, aged 38. Patient has always been healthy; chancre twenty years ago; received local treatment but no other; no secondaries. Apparently well until six months ago; began to walk crooked; no pain; since then very unsteady; mentally cloudy; very sullen in response; vague, tendency to wander.

Physical Examination.—Pupils Argyll Robertson; tongue, lips, tremulous; typical paretic speech; moderate ataxia, writing typically paretic.

Spinal Fluid.—Globulin +; Wassermann ++ in 0.1 c.c. Patient given several injections of mercury, followed by twenty intravenous and nine intraspinal injections of salvarsan. Patient's mental state cleared up very strikingly after the first intraspinal injection. From that time on he continued to improve; after a period of two months without treatment patient returned. Spinal fluid: clear, pressure increased 5 cells, Wassermann negative, globulin +. Blood-serum + to ++. Patient shows signs of relapse after interval of three months.

CASE 66.—J. C. H., man, aged 47. Chancre fourteen years ago; treated; no symptoms; apparently well. Suddenly, fourteen months ago, patient began to be garrulous, talking loud; had delusions of exaltation; went into a state of violent insanity; this occurred on the golf links.

Physical Examination.—Pupils small, unequal; fixed; fine tremor of tongue and facial muscles; no change in speech; knee-jerks absent; general physical condition good.

Spinal Fluid.—Clear, pressure increased; cells 70; globulin ±; Wassermann ++ in 0.1 c.c. Blood-serum ± to ++. Patient given twenty intravenous and nine intraspinal injections. After the first two or three treatments patient became more excitable and violent; after that rapidly quieted down; in three months apparently normal. Spinal fluid then showed normal pressure, clear, cells 5, globulin ±; Wassermann negative throughout. Blood-serum +++. Patient has remained well; back at work; he has been without mental symptoms for a year.

CASE 129.—R. F., man, aged 45. Chancre fifteen years ago; mercury treatment; no secondaries except a few buccal patches; treated steadily until the present. Six years ago paralysis of the eye muscles; two years ago Wassermann +++; one year ago nervous breakdown; depression, despair, nervousness. Spinal fluid: 11 cells, Wassermann +++; globulin +; two or three intravenous injections of neosalvarsan; no intraspinal.

Physical Examination.—Pupils equal, react to light but very little to accommodation; lips tremulous; reflexes exaggerated to clonus; fine tremor of hands; no disturbed sensation; has apprehension, depression, suspiciousness, alternating with excitability and restlessness.

Spinal Fluid.—Twenty-seven cells; fluid clear; pressure low; globulin ++; Wassermann + in 0.1 c.c. Blood-serum 0.1 c.c. +. Under treatment two and one-half months with six intravenous and five intraspinal injections; has been given serum salvarsanated in vitro. After the first intravenous and intraspinal treatment for twelve hours became exalted and quite excitable, very cheerful,

and tremulousness more marked. During the next twenty-four hours slipped back into the depressed state. This has rapidly cleared up. Spinal fluid: at the last examination, clear, pressure normal, cells thirty-two, globulin ++ to +++, Wassermann + in 0.3 c.c.

An analysis of the cases from a clinical and from a serological point of view indicates that the combined method of treatment produced a marked and prompt improvement in symptoms. There is an equally marked effect on the spinal fluid, but one not necessarily parallel to the clinical improvement. The cell-count often falls rapidly, but the Wassermann and globulin tests yield more slowly in most cases. Just as there seems to be no relationship between clinical symptoms and spinal fluid changes before treatment, so during treatment improvement in the two sets of criteria is irregular and uneven. In this, however, is seen again the indication that the symptoms of cerebrospinal syphilis are dependent on the location of the lesion and not on its character.

SUMMARY

Clinically very marked improvement occurs in all groups of cases. In the spinal types pain is usually relieved; ataxia helped in most instances, and not very markedly in a few. The bulbar types and those with fairly pronounced psychic disturbances, depending perhaps on meningeal irritation, show marked improvement in symptoms as well as in spinal fluid. The more definite psychic disturbances also may clear up completely, but their spinal fluids cannot in every case be brought to normal. The cell-count has almost always been reduced in them but the Wassermann test rarely disappears below 0.3 c.c.

In some cases, especially those treated with serum salvarsanized in vitro, transient numbness in the feet has appeared; in other cases a slight failing in general robustness which may be an arsenic effect; and in several instances rather severe pains following the intraspinal injection have been seen. In two cases (76 and 96) there has been a sudden increase in ataxia following a period of definite improvement.

Notwithstanding these undesirable features, the improvement in symptoms in almost all cases is of such striking nature that the method should be given a most careful and thorough study by numerous observers. It is, however, a procedure which must be carried out with the greatest attention to the detail of technic in all its steps, otherwise serious symptoms may be induced. At present there is sufficient evidence to show that it is unsafe to give more than two, or at most three, consecutive injections of serum to which salvarsan has been added directly. In no case should more than 0.0005 gm.

be added. On the other hand, apparently any number of intraspinal injections may be given with impunity when serum salvarsanized in vivo is used.

In those cases which do well the rapid and satisfactory improvement may lead to a premature cessation of treatment. For the elaborateness of the procedure arouses an impulse on the part both of patient and physician to curtail the number of treatments. But with our present knowledge of the significance of syphilitic serological reactions, so long as the spinal fluid or blood gives a positive Wassermann test, the case must be looked on as one potentially capable of relapse. Consequently, no matter how well the patient feels and seems to be, treatment must be continued unremittingly until the laboratory tests are persistently negative.

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THE MECHANISM OF LABYRINTHINE NYSTAGMUS AND ITS MODIFICATIONS BY LESIONS IN THE CEREBELLUM AND CEREBRUM *

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AN EXPERIMENTAL INVESTIGATION

Labyrinthine nystagmus both in clinical practice and in discussions of experimental results is designated in accordance with the quick movement. This is an anomaly, since it reduces to a position of secondary importance the most essential factor in the phenomenon — the cause of the deviation of the eyes, from the primary position of equilibrium[1] or from the primary position of the line of fixation of Listing. It must not be forgotten that the eyes of normal subjects have a definite position when at rest or during fixation. Any involuntary departure from this position means that some unusual influence is operative to cause the deviation, and it is precisely this deviation and influence that the clinician is called on to explain. Various influences acting through the central nervous system may cause such deviation of the eyes from the primary position and each one may act in its own peculiar way. The return to the primary position, if at all possible, is likely to be much more uniform than the manner of deviation from the normal. In labyrinthine nystagmus as we have elsewhere described it,[2] the slow component is of labyrinthine origin, and hence is of most significance so far as its relation to the labyrinth is concerned. Variations in the manner of the quick return indicate disturbance in the oculomotor rather than in the labyrinthine or vestibular mechanism. In labyrinthine nystagmus both the slow deviation and quick return are a coordinated series of associated movements, involving contraction of certain groups of muscles and at a certain stage of the process, relaxation of their antagonists, as Bartels'[3] experiments demonstrate.

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1. Sherrington: Integrative Action of the Nervous System, New York, 1906, p. 279.

2. Wilson and Pike: Philosophical Trans. Royal Soc., 1912, p. 127; also Proceedings Soc. Exper. Biol. and Med., 1913, x, 81.

3. Bartels: Ueber Regulierung der Augenstellung durch den Ohrapparat, Arch. f. Ophth., lxxvi, 1; lxxvii, 531; lxxviii, 129; lxxx, 207.

Without lesions in other parts of the central nervous system, there is no double vision at any period. Only when some intracranial complication or oculomotor paralysis exists does double vision arise.

Uhthoff[4] distinguishes two varieties of nystagmus: 1. Nystagmus (Bartels', *Pendelnystagmus*), a pendulum movement of the eyes in both directions from the central point of rest. 2. Nystagmus twitching (Bartels' *Rücknystagmus*) when the movement is quicker in one direction. English writers have generally applied the term nystagmus to all oscillations of the eyes without distinction in regard to the variety of the movements. Occasionally the term nystagmus twitching or nystagmoid movement is used to distinguish the more irregular types.

Various mechanisms for nystagmus have been postulated from time to time. Wundt postulated a center for the afferent impulses from the soft parts of the eyes in the cerebellum. As we have shown, however, typical labyrinthine nystagmus may be observed after complete removal of the cerebellum. Bárány has located a nystagmus center in the angular gyrus, and at some point above the oculomotor nuclei, possibly in the pons.[5] Marburg has postulated a nystagmus center in Deiter's nucleus, basing his conclusion on the fact that lesions of Deiter's nucleus, when the rest of the encephalon is supposedly intact, give rise to nystagmus.

Two general objections may be urged against the various hypotheses so far advanced. The first is that writers often assume that, if nystagmus arises from a lesion of a particular region, that region is a center for nystagmus. A lesion of Deiter's nucleus, for example, is merely a lesion of one part of the central portion of the vestibular tract, and nystagmus would naturally arise from such a lesion, just as it does from lesions of the membranous labyrinth of the ear or from intracranial section of the vestibular nerve. The second objection is that little regard has been paid to the whole complex motor mechanism of the eyes, which cannot be described in terms of circumscribed isolated centers, but which must be described in terms of an integrative mechanism or system.

In the consideration of nystagmus after unilateral labyrinthine destruction we are met at the outset with two series of facts. First, nystagmus does not occur in many of the lower vertebrates, but in all of these vertebrate types with movable eyes so far examined, a deviation of the eyes does occur, and this deviation in the lower forms is permanent. Second, nystagmus does occur in the higher vertebrates, but neither nystagmus nor deviation is permanent. In considering,

4. Uhthoff: Augenerkrankungen bei Erkrankung des Nervensystems, Graefe-Saemische Handbuch d. ges. Augenh., Section Rückenmark, Part 2, 1904, v, 3.
5. Marburg: Neurolog. Centralbl., 1912, xxxi, 1366.

therefore, the mechanism of nystagmus in the higher vertebrates, we have to explain why neither nystagmus nor deviation of the eyes is permanent in these forms.

In the vertebrates, nystagmus after stimulation or unilateral labyrinthine removal varies as a rule in intensity with the position of the animal in the vertebrate phylum. Its intensity is greatest in the mammals. In Petromyzon it is not present, nor does it appear in the frog and the turtle. Some, however, believe that small compensatory movements of the eyes may be observed in the frog. In the cartilaginous fishes it is absent in many forms, e. g., dog-fish. When present, careful observation is required to demonstrate its presence, both in the cartilaginous and in the bony fishes. Ewald[6] showed its presence in pigeons, but so far as our observations go, it is slight and less pronounced than in mammals.

There are definite reasons which lead to the separation of the two phases in nystagmus in regard to cause and source.

1. The deviation alone occurs under an anesthetic. The quick phase only appears as the effect of the anesthetic begins to wear off, and the animal regains consciousness.

2. When the anesthetic is pushed, the slow deviation is one of the last of the phenomena about the head to disappear, and persists nearly or quite as long as the corneal reflex.[2]

3. Bartels has shown that the slow phase alone can be produced by rotation in sleeping children, and that in prematurely born children (7 months) the slow deviation alone can be elicited for some time after birth.

4. We have shown in a previous paper[2] that the quick phase can be eliminated by destruction of the cerebrum and thalamus while the slow persists. As there pointed out, it appears to us that the paths along which the slow deviation occurs are fairly definitely established. We have shown that the slow deviation persists when the animal is at least partly under the influence of a narcotic.[2] Where and how far in their course the vestibular fibers cross the middle line between the labyrinth and oculomotor nuclei has not been established. Loeb's experiments and Bartels' work would seem to indicate a crossing, while the anatomical work of Winkler appears to indicate that the crossing is only partial.

We have endeavored to throw some light on the question by splitting the pons and medulla in the middle line in dogs. So far these experiments tend to substantiate Winkler and our already published hypothesis, since they show that there is no crossing of fibers from the

6. Bartels: Ueber Regulierung der Augenstellung durch den Ohrapparat, Arch. f. Ophth., 1910, p. 17-21 and p. 51.

vestibular nerve in the anterior two-thirds of the pons and whatever crossing occurs is in the region of the nucleus of the sixth nerve.

Having determined that in labyrinthine nystagmus we are dealing with a double movement in which the slow deviation can be definitely separated by experiment from the return movement, we now look for the source of the quick backward jerk. There are several possibilities of its origin.

We may suppose that the quick backward jerk arises in response to impulses which tend to pull the eye back so that the visual images will fall on a particular retinal field (Wundt). Two series of facts militate against such an hypothesis. Nystagmus occurs in blind subjects when the lesion is in the retina or some part peripheral to the terminations of the optic nerve in the central system[7] when placed on the turning table, or when the ears are irrigated with hot or cold water. And, as we have shown,[2] nystagmus quickly returns when one or both occipital lobes of the cerebrum are removed. Hitzig also noticed nystagmus in blind tabetics.[8]

A second possibility is that the abnormal deviation of the eyes sets up sensory impulses in the afferent endings of the eye muscles themselves, which bring about a return, either reflex or voluntary, of the eyes to the normal position. Nystagmus would then be a response to kinesthetic sensations. We consider this the more probable hypothesis, supported as it is by some observations we have made on third nerve paralysis. It is an hypothesis closely akin to that of Bartels. We have then to trace out the relation of this movement to the cerebrum or thalamus. Bartels' observations on prematurely born children indicate that it involves a path which becomes medullated relatively late.

In comparing the deviation of the eyes which occurs after cortical stimulation with the deviation of the eyes which results from labyrinthine stimulation, it would appear that the relaxation of the antagonistic muscles is not the same in the two cases. Thus from Sherrington's[9] observations it would appear that in cortical stimulation the contraction of a muscle is equal to and balanced by the relaxation of its antagonists. That this is not the case in stimulation of the labyrinth a consideration of Bartels' diagrams[3] appear to show. Here the amount of relaxation in the antagonist falls behind the amount of contraction in the prime mover. As a result we believe that in the deviation of the eyes from labyrinthine stimulation a strain is put on the antagonistic

7. Mulder: Arch. f. Ophth., 1875, xxi, 68.

8. We hope to show in a later paper that these objections are not so fundamental as sometimes has been supposed. This may be inferred from what is stated in the second last paragraph of this paper.

9. Sherrington: Integrative Action, p. 279; Proc. Royal Soc., London, 1913, lxxxvi, 225 and 1893, p. 407.

eye-muscles, which strain does not arise in movement from cortical sources. This strain produces a feeling of unusual or uncomfortable position which, when the sensory and motor systems are intact, results in a return to a more comfortable position. The return of the eyes to the median position would on such a hypothesis, be of exactly the same nature as the return of a dog's hind foot from an uncomfortable position when the sensory and motor systems are intact.

We have attempted to locate a region where a lesion consistently affects or abolishes the quick component of nystagmus arising either as a result of destruction or stimulation of the labyrinth. We have pointed out in a previous paper that such a region does not exist in the cerebellum. As there shown, the removal of the lateral lobe or of the vermis or of the whole cerebellum may affect, but does not abolish, the nystagmus which follows labyrinthine destruction. Since these results were published, we have repeated in detail these experiments and with the same result. Accordingly, we feel justified in saying that neither the slow deviation nor the quick return has any necessary pathway nor any indispensable center in the cerebellum.

We have previously pointed out that, in cats and dogs, complete decerebration, including the corpora striata and the thalamus, wholly abolishes the quick component after labyrinthine stimulation or removal, although the slow deviation of the eyes persists. We are unable to confirm Bauer and Leidler[10] who report the occurrence of nystagmus after removal of all parts of the cerebrum as far down as the corpora quadrigemina. A number of new experiments substantiate our former conclusions. The quick movement in nystagmus arises from some mechanism above the corpora quadrigemina — a point in which we confirm Bartels' view. The question becomes, then, whether the quick component of nystagmus arises from the thalamus or from the cerebrum. Anatomically, afferent tracts pass from the eye-muscles back to the oculomotor nuclei, and then, in all probability, through the thalamus where they are relayed, and then on up to the cerebral cortex. Efferent tracts arise in at least three different regions of the cerebral cortex and pass down to the oculomotor nuclei. It appears to us that the mechanism of nystagmus involves cortical cells and areas, and that any return of nystagmus after injury to a part of the cortical mechanism may be explained by supposing that the shorter, more primitive paths through the subcortical regions become passable for nervous impulses.

In assuming that the mechanism of nystagmus involves thalamic paths and nuclei alone, we meet with certain difficulties in arriving at a satisfactory explanation. We must explain why, when every other part

10. Bauer and Leidler: Arbeit. a. d. Wien. Neurol. Institut., 1911, xix, 155.

of the efferent oculomotor path is open, as shown by the presence of the corneal reflex, and the slow deviation of the eyes in response to labyrinthine stimulation, the path involved in the production of the quick movement should be the only one to be blocked. The explanation of shock does not explain anything until we tell what shock is. A hypothetical principle of explanation which in the last four decades of investigation, has proved so confused and conflicting, as shock, and which follows no laws so far discovered, and apparently, no discoverable laws, is not likely to lead us far as a constructive principle. We may point out that shock if present at all, follows the same general course with reference to nystagmus that it follows in the case of the skeletal muscles generally; that is, it is exerted on the afferent pathway, since, to all our tests, the efferent path is so obviously open.[11]

We may assume, then, as a working hypothesis, that some cerebral mechanism is involved in the production of the quick phase of nystagmus, and it remains to trace out as far as possible the regions and tracts concerned. There are two possibilities: 1. Both cerebral hemispheres may be involved in the production of the quick phase of nystagmus when the slow component is in a given direction. 2. Only one cerebral hemisphere may be involved. If only one is involved, what relation does it bear to the direction of the slow or labyrinthine phase? Experiment shows that the second possibility is more nearly the true one so far as the lateral movement is concerned. Space does not permit the recital of the details of the experiments at this time, and a brief presentation must suffice. This conclusion is based on the following:

1. The results of removal of one labyrinth and one cerebral hemisphere, noting the presence or absence of nystagmus.

2. The results of electrical, caloric and rotation tests in such animals.

3. The results of electrical, caloric and rotation tests in animals in which both labyrinths are intact, but in which one cerebral hemisphere had been removed.

As a general result, we may state that complete removal of the cerebral hemisphere on the side of the slow deviation abolishes all except a small rotatory component of the quick phase of nystagmus. Complete removal of the cerebral hemisphere of the side toward which the quick component is directed has but little effect on the quick movement.

Rotation, electrical and caloric tests on such animals again show the dropping out of the quick phase of nystagmus when the slow deviation of the eyes is directed toward the side of the cerebral lesion, and

11. Pike: Am. Jour. Physiol., 1909, xxiv, 124.

little or no effect when the slow component is directed toward the uninjured side of the cerebrum.

We may here note in passing that injury to the anterior corpus quadrigeminum of the side to which the slow deviation of the eyes is directed does not abolish the nystagmus, either in its slow or quick phase, but it does bring about a dissociation of the eye movements.

These tests, when repeated on animals with both labyrinths intact, but with removal of one cerebral hemisphere, lead to the same conclusion.

We have attempted in cats, dogs and monkeys to find some region in a hemisphere where a lesion will modify or abolish the nystagmus which follows stimulation or destruction of the labyrinth. In the course of the experiments we have removed the various areas of the cortex, frontal, parietal, occipital and temporal, and have also at times destroyed the subcortical ganglionic masses. Having destroyed these areas, we have then stimulated one or both labyrinths with the electrical current, with hot and with cold water and by rotation. We have also in many of these cases destroyed one labyrinth either concomitantly with or subsequent to the cerebral lesion — a labyrinth either on the side of or opposite to the cerebral lesion. We cannot at this time enter into the details of the results, which will be published in full later, but we desire to state here that the only region where we obtain consistent alteration of the labyrinthine stimulation, and that only so far as the quick component is concerned, is the region of, or adjacent to, the temporal lobe. In these cases we found that stimulation of the labyrinth on the side opposite the cerebral lesion with cold water or with the anode gave typical labyrinthine nystagmus, lateral in character, while stimulation with hot water or the cathode gave deviation, but no lateral nystagmus. We also found that destruction of the labyrinth on the side of the cerebral lesion gave no nystagmus. There was further noted in some of our cases that the eye on the side of the lesion showed a rotatory movement around an anteroposterior axis, while this movement was wanting in the eye of the opposite side.

To sum up, our idea of the mechanism of nystagmus is first, an agency somewhere which produces a deviation of the eyes from the primary position of equilibrium or the primary position of the line of fixation of Listing. In labyrinthine nystagmus, this agency lies in the labyrinth. The internal rectus muscle on the side of the slow deviation and the external rectus on the opposite side are subjected to a strain greater than usual. This strain, resulting in the stimulation of the sensory or afferent endings of the eye-muscles, sets up afferent impulses which are conveyed to the cerebrum over the afferent fibers

in the third, fourth and sixth cranial nerves.[12] These afferent impulses in their turn set up efferent impulses in the oculomotor cells of the cerebrum, which result in a quick, jerky contraction of the internal rectus on the side of the slow deviation and of the external rectus of the opposite side, with relaxation of the antagonistic muscles. The effect is a restoration of the eyes to the primary position. The eyes do not go beyond this median position when the cerebrum is intact, since the afferent impulses to contraction of the external and internal rectus muscles concerned cease when the eyes reach this position of equilibrium.

Lesions of the cerebral hemisphere on the side of the slow deviation of the eyes abolish or reduce the quick component, since it is from the hemisphere of this side that the efferent impulses concerned in the pulling of the eyes back to the median line arise.

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12. Tozer and Sherrington: Receptors and Afferents in Third, Fourth and Sixth Cranial Nerves, Proc. Royal Soc., 1910, p. 450.

THE RELATION OF PANCREATIC ORGANOTHERAPY TO KETOGENESIS *

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I. INTRODUCTION

The earlier trials, both laboratory and clinical, of pancreatic opotherapy, were conceived and undertaken at a time when the ground-problems of diabetes — almost coextensive as they are with the whole domain of pathometabolism — were not so clearly defined as at present. Nevertheless, on historical consideration of these attempts it becomes obvious that the propelling forces behind them all were, first, the urgent demand for a successful therapy, and, following that, the vague assumption, dating from or even antedating von Mering and Minkowski's classic work, that the pathogenetic basis of the clinical entity diabetes is the absence or deficiency of a pancreatic hormone or internal secretion necessary in some sense to carbohydrate utilization. Whether this basal assumption of an internal secretion shall prove valid or not, it is certain that the attempts at pancreatic organotherapy have amply justified themselves, not as yet by realizing much of practical value to the clinician, but by virtue of the increasing light they have thrown on the problems of general and of diabetic metabolism.

The earlier workers in this domain contented themselves largely with the investigation of the effects of various types of opotherapy on the most obvious symptom of diabetes, namely, *glycosuria*. Only recently has the work — or some of it — become more critical in the sense of adopting more fundamental criteria, such as the effect on glycemia and on the respiratory quotient.

Here, as in all such problems, it has taken much continued effort to eliminate irrelevant, interfering factors, which have vitiated results and invalidated researches; for example, many of the pancreatic extracts used have been of an acid reaction, regardless of the fact that this physical condition, per se, influences greatly the state of hepatic glycogen, and hence the glycosuria. Again, many investigators have selected one type of opotherapy (as injections or transfusions) to the exclusion of other types, and apparently at random, that is, without due consideration of the reasons for so choosing.

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Correlating the many researches, however, the influence of pancreatic opotherapy on *carbohydrate metabolism* has, at least in some of its aspects, been rather minutely investigated. In contrast, there are in the literature only casual references to the influence of organotherapy on the formation and excretion of *ketone bodies*, and it has been the intent of the present work to investigate this relation more precisely.

As it is particularly in the complex field of diabetes that progress has been so hampered and retarded by preconceived theories, it seemed best to attack each segment of the problem unprejudiced by any general, hypothetical concepts. Hence, all unproved assumptions as to an internal pancreatic secretion, its nature, or even its existence have been insistently avoided. Also a neutral ground as to the importance of the ketone bodies for the clinical picture of diabetes has been assumed. There is at present no certainty as to whether "acidosis" is a complication of diabetes, or an integral part of the deranged functioning, as to whether the ketones are the cause of coma diabeticum or merely harmless by-products of the essential vicious metabolism. Accordingly, in the introductory bibliographic interpretation given below I have sought to eliminate all unproved dogmas, and to keep within the bounds of objective data.

II. HISTORICAL AND CRITICAL

Any investigation of the influence of pancreatic organotherapy on ketogenesis must obviously take into account, at every step, the allied problem of the effect of such opotherapy on glycosuria and on the general constitutional condition; this because of the close relationship subsisting between carbohydrate metabolism and "acidosis." I shall accordingly, in conformity with the following schema, briefly review the past work along each of these lines:

1. Effect of pancreatic opotherapy on glycosuria and the general condition.
   - (*a*) Feeding.
   - (*b*) Injections.
   - (*c*) Transfusions and parabioses.
   - (*d*) Grafts and transplants.
2. Effect on ketoplasia and ketogenesis.

EFFECT OF PANCREATIC OPOTHERAPY ON GLYCOSURIA AND THE GENERAL CONDITION

(a) Feeding of Gland and Its Extracts and Ferments

When dogs suffering from chronic, pancreatic diabetes are fed with raw pancreas, the glycosuria increases three- or four-fold; cooked

gland gives negative results.[1] The feeding of raw muscle and other tissue extracts exerts a similar augmentative effect on the glycosuria.[2]

Fresh pancreas (of sheep, calf or fish) in human diabetes has given either negative results, sometimes accompanied by slight subjective (psychic) improvement,[3] or else an actual increase of glycosuria.[4] The feeding of pancreatin also causes greatly increased glycosuria.[5]

Positive results are few and questionable. Ausset[6] claimed lowering of glycosuria and even complete "cessation of diabetes" in diabetic dogs and man fed on cooked pancreas. In one group of cases, however, namely, the diabetides of distinctly pancreatic type with deficient fat and protein absorption, there seems to be abundant evidence of improvement in absorption and general nutrition following exhibition of pankreon,[7] or of raw sheep pancreas.[8]

As to the influence on carbohydrate tolerance in this group of cases, Wegele and Meyer claimed an improvement, while Mosenthal in his carefully controlled observations denies any effect. Pratt, Spooner and Murphy[9] induced in dogs the chronic diabetes of slowly progressive pancreatic atrophy, with lowering of dextrose tolerance and markedly decreased absorption of fats and proteins. Raw sheep pancreas was then administered over prolonged periods. In general, fat and protein absorption were improved, and in one animal the carbohydrate tolerance was greatly increased. Even in this case, however, the tolerance could not always be raised; moreover, in other dogs this influence was slight and in a late case[9] negligible.

With regard to the treatment of diabetes by feeding acid extracts of duodenal mucosa or secretin, a few authors[11] have claimed improvement, but most observers report negative results.[12] Altogether the destructive criticism of Pflüger[13] and Leschke,[14] which showed most such results to be the expression of fluctuations common to all non-total diabetics, seems to be applicable also to the later results, but with the exception noted above — namely, the positive influence on digestion and assimilation in *pancreatic* diabetes. Moreover, lessened glycosuria when observed is almost certainly due at times to a toxic lessening of renal permeability, the hyperglycemia not being decreased (see below).

(b) Injections of Pancreatic Extracts and Ferments

Intraperitoneal injections of emulsions of fresh pancreas in depancreatized dogs sometimes cause marked drops in glycosuria.[15] But all such effects are due to a peritoneal irritation with reflex *decrease* of *renal permeability*.[16] No improvement results in human diabetes from intraperitoneal injection of emulsions.[17] Repeated large doses given to guinea-pigs and depancreatized frogs by the peritoneal and also by the combined subcutaneous and peritoneal routes not only result in no

improvement of the diabetes, but are actually very toxic and uniformly increase glycosuria. Extracts inactivated by heat give negative results.[14]

Subcutaneous injections of pancreas may cause marked drops of glycosuria in human diabetes,[18] and in the pancreatic diabetes of dogs.[19] Certain pancreatic extracts given subcutaneously cause diminished glycosuria in the epinephrin — and phloridzin — diabetes of animals.[20] But such reductions of glycosuria are always associated with general, constitutional depression or with decreased renal permeability,[21] the latter accompanied by increase of blood-sugar.[22] There is also abundant evidence that diabetes is not ameliorated in any of its aspects. Thus, subcutaneous injections of extracts give negative results in human diabetes.[23] In depancreatized dogs they give similarly negative results,[24] and even cause a toxic increase of glycosuria.[25] Leschke[14] verified this for guinea-pigs and depancreatized frogs. Indeed, subcutaneous injections of extracts of almost any organ cause toxic effects and a glycosuria (liver, spleen, heart, kidneys, pancreas, skeletal muscle[26]).

Intravenous injections also give therapeutically disappointing results. Thus, Williamson[17] observed no influence over human diabetes, and Hédon,[27] working on diabetic dogs, observed no improvement, while his tables actually show a glycosuric effect. Zuelzer[28] administered his "hormone" of dog pancreas intravenously to depancreatized dogs and human diabetics. The resulting temporary decreases in glycosuria and ketonuria are admittedly secondary to the marked constitutional (toxic) depression.[29] Alcoholic extracts administered intravenously give negative results; aqueous extracts cause transient lowering of glycosuria and dextrose-nitrogen ratio, but this is interpreted as a toxic depressor action rather than as specific regulatory.[30]

It seemed at first that extracorporeal perfusions, while not strictly opotherapeutic, might throw light on the problem. Thus, the addition of pancreatic extracts to blood perfused through the beating heart caused a marked disappearance of dextrose, which was thought to be due to the "pancreatic hormone."[31] This view is now abandoned.[32] The sugar disappears not through oxidation, but by polymerization.[33] Other fallacies are also inherent in the perfusion methods as applied to pancreatic opotherapy.[34] Thus slight changes in reaction affect the storing of glycogen;[35] also slight changes in the concentration of K-ions influence the disappearance of sugar from the blood.[36] When pancreatic extracts are added to the blood perfused through isolated surviving livers, there does not appear to result any increased deposit of glycogen or any diminished glucose production.[37]

Two recent researches are of especial importance because based on the realization that fluctuations in glycosuria are of manifold significance, owing to the complexity of the factors which may influence them and that the final test of a "hormone" will be the restoration of pancreatic function to the entire organism, the best criterion being conceived to be the respiratory quotient. Thus[38] pancreatic extracts given intravenously and subcutaneously to depancreatized dogs exert no influence on the respiratory quotient. After large injections there is sometimes a temporary fall of glycosuria due to decreased renal permeability, but soon followed by a compensatory rise.

Feeding or injections of *diastase* probably have no relation to pancreatic opotherapy, since it is not a function of the pancreas to deliver diastatic ferment to the blood.[39] Moreover, the lowered glycosuria sometimes following intravenous injection of diastase[40] is certainly secondary to the general systemic depression.[14]

According to some observers there results an actual increase of glycosuria on intravenous or subcutaneous injections of diastase,[41] or of pancreatic juice.[42]

(c) Transfusions and Vascular Parabioses

When pancreatized dogs receive transfusions of fresh blood from normal dogs their glycosuria is sometimes uninfluenced,[43] but more often is temporarily decreased.[44] Fresh, defibrinated blood gives the same result.[45] The hyperglycemia is not reduced.[46]

Similar results follow the crossing of circulation between normal and diabetic dogs by vascular parabioses. This is true no matter what vessels are anastomosed, but the reduction of glycosuria is greatest when the blood passes from the pancreatic circulation of the normal into the systemic circulation of the diabetic dog.[47] However, this reduction of glycosuria has no relation to specific opotherapy. It is due to a temporary, toxic decrease of renal permeability, as Hédon himself admits in his last papers.[48] It is associated with oliguria and albuminuria, and with general constitutional disturbances—fever, anorexia and marked depression. The hyperglycemia is either increased (normal dog) or not reduced (diabetic dog). Moreover, a few hours after such transfusion there occurs a compensatory rise in dextrosuria, balancing the temporary reduction.[49]

The introduction of foreign bloods and serums per se is partially responsible for these toxic phenomena. Thus in Hédon's experiments the normal dog became immediately glycosuric and hyperglycemic, and when two totally diabetic dogs were joined both developed oliguria and reduction of glycosuria, and both invariably died. Pancreatic extracts have been repeatedly shown to decrease renal permeability to

dextrose,[50] but Hédon's last experiments make it probable that the toxic effect on renal permeability is due to the foreign serums.

When the more fundamental criterion of respiratory quotient is invoked, it is found that the transfusion of large amounts of fresh, defibrinated blood, or whole blood, from normal to diabetic dog gives rise to no change in the respiratory quotient, and presumably no increase in the oxidative capacity of the organism. Crossed circulations are also negative in the same sense.[35] A similar toxicity of transfusions for the *human* diabetic is strikingly shown by the case of Raulston and Woodyatt,[51] who directly transfused blood from a normal man to his diabetic brother. The diet and metabolic data had been carefully controlled for months. The result was a marked (late) increase in dextrosuria, and in ketonuria. There was no evidence of improved carbohydrate utilization, and the authors believe blood transfusions to be definitely contra-indicated in severe diabetes.

With reference to the use of lymph Biedl, after reviewing the literature,[52] concludes on the basis of original experiments that intravenous and subcutaneous injections tend to lower the dextrose-nitrogen ratio.

(d) Grafts and Transplants

The extirpation of all the pancreas except a small lobe of the processus uncinatus, with subcutaneous implantation of the latter,[53] its vascular pedicle being preserved, is generally referred to as a "transplantation,"[54] but is rather an incomplete pancreatectomy with dislocation of the remaining fragment. Rarely such a lobe lives and functionates after cutting of the vascular pedicle, through establishment of secondary vascularization from the local tissues.[55] This amounts to an autotransplant, but is equivalent, from the point of view of organotherapy, merely to any incomplete pancreatectomy.

Many attempts at heterotransplantation and homotransplantation have failed.[56] Carrel,[57] in his latest address, shows on general grounds that *auto*transplants of organs are often viable, *homo*transplants or *hetero*transplants practically never.

Autotransplants of part of the pancreas into the spleen, the rest of the pancreas being extirpated, have succeeded, as shown by their ability to prevent the total diabetes. These have been *free*[58] or pedicled with subsequent severing of the vascular stalk.[59] The undoubtedly successful functioning of such autotransplants without pedicle teaches us no more than Lombroso's original experiment.

These procedures seem directly comparable with the extirpation of the hypophysis and immediate reimplantation into the cerebral cortex, with prolongation of life and viability of the graft for over a month.

In this case, too, the *glandular deficiency* is established; otherwise the autotransplant will probably not take.[60]

Forschbach[61] united dogs parabiotically, bringing peritoneal cavities and homologous layers of the parietes into continuity. There was *no vascular* continuity, and hence this procedure is the equivalent, not of transfusion or of crossed circulation, but of transplantation. On extirpation of the pancreas of one, the ensuing glycosuria was slight and developed late. The normal dog developed a (toxic) glycosuria. The wounds healed well and no diabetic cachexia developed. When the animals were separated, the depancreatized dog soon died of infection or cachexia.

If the pancreas of a pregnant dog near term be removed no glycosuria develops; after delivery it becomes intense at once.[62] Are these last two observations to be explained on the basis of internal secretion or of toxic effects on renal activity?

Summary

To summarize with reference to the effect on glycosuria, the general constitutional condition, and the carbohydrate oxidative power of the organism:

1. *Feeding* of fresh pancreas has usually been observed, both clinically and experimentally, either to have no effect on, or else actually to increase the glycosuria. This action is hardly specific for pancreas, being induced by many raw tissues. It is doubtful whether carbohydrate tolerance has ever been increased. Good effects as to increased absorption of fats and proteins and improvement of nutrition must be conceded. Unfortunately, glycosuria has been made, in all feeding experiments, almost the sole criterion of the influence on carbohydrate utilization.

2. When, after *injections* of extracts and emulsions, lessened glycosuria occurs, it is referable to general systemic depression or to decreased renal permeability. Intraperitoneal injections are absolutely fallacious, because of the renal reflex. Under many conditions there is even a markedly increased toxic glycosuria. Adjudged by the most reliable criterion (respiratory quotient) the effects on carbohydrate intermediate metabolism are nil.

Injections of enzymes (diastases) also cause a toxic increase of glycosuria, but sometimes a temporary decrease of glycosuria associated with systemic depression.

3. *Transfusions* and *crossed circulations* always have a toxic action. Sometimes the glycosuria is temporarily reduced, in which case there are either associated symptoms of general depression, or else evidence of reduced renal function (albuminuria, oliguria, later compensatory

rise of glycosuria). Sometimes there is a toxic increase of glycosuria, of ketonuria, and of toxic products of protein catabolism. Hyperglycemia is not decreased. There is no rise in the respiratory quotient. The reaction is bad in every sense as to the general systemic effect.

4. The successful (auto-) *transplants* show merely what was known from Lombroso's original experiment, namely, that if a living, functioning fragment of the animal's own pancreas of sufficient size be present in the blood circuit, diabetic symptoms will be inhibited.

The parabioses (Forschbach) and the pregnancy experiments (Carlson) seem to be the equivalents, from the opotherapeutic point of view, of *homo*transplants. In each case there was established a pancreatic insufficiency of one animal, and an attempt to remedy this by supplying the products of the pancreas of another individual of the same species. It is noteworthy that in only these two of many researches was an opportunity afforded, by virtue of the absence of vascular continuity,[63] for intimate interchange (parallel to osmosis of crystalloids), without an actual mixing of foreign bloods or serums. And in these two researches we possibly have some evidence of the influence of a pancreatic hormone over the fundamental causative processes of diabetes. In Forschbach's experiments the reparative functions of the diabetic animal were good, which is much more significant than any reduction of glycosuria. Even here there is the possibility of a toxic reduction of glycosuria.

Factors Influencing the Degree of Glycosuria

It is evident that the *degree* of *glycosuria* observed in any given opotherapeutic experiment is a *resultant* of *several* opposing factors, some tending to increase, others to decrease it, and probably none to be interpreted as really therapeutic in the sense of exerting any curative influence on the underlying metabolic error of diabetes. Some are more in evidence on parenteral, others on enteral administration. It is possible to designate roughly some of these factors:

A. Lessening glycosuria.

(*a*) Toxic decrease of renal permeability.[64]

(*b*) Decrease of glycosuria associated with general constitutional depression (as obviously in Zuelzer's hormone work), comparable to the decrease of glycosuria and ketonuria observed in moribund diabetics.

(*c*) It has been definitely shown that acidity or alkalinity of the extract per se may exert a marked effect on glycosuria and on glycemia, through its influence on the state of hepatic glycogen. Administration of even dilute acids mobilizes hepatic glycogen, alkalies exerting the reverse effect.[65]

B. Increasing glycosuria.

(*á*) The opinion has very generally been held that the increased glycosuria observed on *feeding* of pancreas may be due to *bettered absorption*, especially of carbohydrates.[66] That other factors are at work is shown by the fact (Sandmeyer) that even after decrease of daily rations of diabetic dogs by 50 per cent., the glycosuria increases on pancreatic feeding from three to tenfold.

(*b'*) There is certainly a *toxic glycosuria*, or perhaps several types. And it is sometimes, if not always, accompanied by hyperglycemia. Even the increased glycosuria of pancreatic *feeding* has been interpreted by some as toxic, rather than due to increased absorption,[67] Reach having proved that it is not due to better digestion or assimilation. The toxic split products of proteins are held to be the responsible agents, and this seems probable, inasmuch as the feeding of various amino-acids to diabetic dogs (both depancreatized and phloridzinized) and human diabetics results in a toxic increase of glycosuria.[68] The increased glycosuria of *parenteral* opotherapy is almost certainly toxic. Leschke[14] believes enzymes (for instance, trypsin) to be the agent, but hints at the possibility of non-catalytic (chemical) toxins.[69] It is possible that the glycosuria and the toxic (or lethal) phenomena have different agents.

As to the point of attack of such a glycogenic toxin, one can at present only speculate as to whether the action is through increased hepatic glycogenolysis (mobilization of glycogen), toxic lowering of the general tissue oxidative capacity, increased renal permeability, or some other mechanism.

After repeated large injections of gland extracts (pancreas, thyroid, liver, kidneys, etc.), there develop no micropathologic changes *specific* for the various extracts, but in all cases, parenchymatous degenerative hepatitis and nephritis with perivascular infiltrations, hyperplastic follicular splenitis and hyperplasia of lymph-nodes.[70]

(*c'*) Finally, as a possible explanation of increased glycosuria, Cohnheim and Klein† note that the foods causing the greatest flow of pancreatic juice (raw meats) are the ones causing glycosuria. They suggest that the internal and external pancreatic secretions are likely to vary inversely as to their potency, and that hence the increase in external secretion will be correlated with a decrease in internal secretion, even to the point of producing glycosuria. Of course, this is speculative.

Historically it will be noted that really positive results of opotherapy have receded as the criteria have become more exacting. Attention was earlier focused on the glycosuria, and to a lesser extent

†. Cohnheim and Klee: Ztschr. f. physiol. Chem., 1912, lxxviii, 464.

on the general clinical condition. Of late more stress is being given to the true indices of carbohydrate oxidative power, and in the near future even heavier demands will be made on any attempt to establish the claims of an opotherapy, in conformity with the growing tendency to discard the assumption that the disturbances of carbohydrate intermediary metabolism constitute the sole essence of the entity diabetes.[71]

INFLUENCE OF PANCREATIC OPOTHERAPY ON KETOGENESIS

Only a few isolated and conflicting observations are recorded in the literature. Salomon[72] observed an increase of acetonuria after the use of pankreon in a case of pancreatic diabetes.

Sandmeyer[73] observed in his chronic diabetic dogs that the feeding of *raw* pancreas caused increase of glycosuria (see above) with appearance of acetone and diacetic acid. The latter was noted twice,[74] and *only* on administration of raw pancreas. No quantitative determinations were made.

Zuelzer,[28] using the hormone referred to above, in depancreatinized dogs and moderately severe human diabetes, observed lessened "acidosis," as indicated by the color intensity of qualitative tests of urine. But Forschbach[75] invalidates these conclusions just as he had their deductions as to decreased glycosuria (see above), on the ground of the general toxic depression. Moreover, he observed *no decrease* of ketonuria, even with the marked constitutional reaction.

Mosenthal,[76] in a single case of human diabetes, probably of pancreatic type (displaying deficient fat and protein absorption, with large fatty stools and undigested meat fibers), found that on a regimen of raw sheep pancreas feeding, the urinary ammonia was greatly increased, for example, from about 2.2 gm. on ordinary diet to about 5.2 gm. after exhibition of pancreas, this rise being associated with a corresponding increase in ketonuria, the beta-oxybutyric acid rising from 2.2 gm. to 32.1 gm. Mosenthal's observations were clinical, and in a particularly severe case,[77] it became necessary, on considerations of safety, to interfere with the experiment in such ways as to detract from the clear-cutness of the interpretation. Thus, the use of opotherapy had to be frequently interrupted; alkalies were administered from time to time; also there is some ambiguity as to the amounts of fat fed, and the influence of other food elements. This is not mentioned in a spirit of criticism, as the duty to the patient obviously had to take precedence of the research. The great interest in Mosenthal's report lies in the fact that the feeding of raw pancreas gave rise to tremendous ketonuria in a case of undoubted "pancreatic diabetes." Under the opotherapy there was, except for the (at times alarming) increase of ketogenesis, a marked general improvement, and certainly increased utilization of fats; thus "the stools changed from those

typical of pancreatic disease to what appeared to be normal movements." He concludes that the increased ketogenesis is due to increased intestinal absorption of fats. He evidently believes (following most authors) that dogs totally pancreatic-diabetic excrete no ketones, and explains this on the basis of non-absorption of fat. This question is examined below.

Raulston and Woodyatt,[51] in their clinical research described above, noted, on direct transfusion of blood from normal to diabetic man, a marked increase of ketonuria. The total beta-hydroxybutyric acid increased from 190 gm. for the five days preceding, to 273 gm. for the five days following. Their metabolic work seems perfectly controlled as to diet and other factors. Dakin and Dudley[78] perfused dogs' liver with blood containing added substances, known from Embden's experiments to yield aceto-acetic acid freely under these conditions, as tyrosin, the sodic salts of butyric and homogentisinic acid. To this perfusing blood were then added fresh extracts of pancreas, or heated pancreatic extract of skeletal-muscle extract, all prepared by grinding the fresh tissues in water. No decrease in hepatic ketogenesis resulted. Their conclusion is that they have found no evidence that the pancreas furnishes an enzyme or hormone, the absence of which leads to acidosis in the diabetic animal.

III. METHODS

A. CHOICE OF ANIMALS; ACIDOSIS IN DOGS

In undertaking a research on "acidosis" the selection of an animal is a matter of great importance. In general diabetic work, the dog has been, of course, at once the most available and most useful. But where any consideration of ketogenesis is concerned, one must raise the question as to whether a carnivore is suitable, the opinion being somewhat widespread that there is some fundamental difference in the reaction of dogs and man to factors of ketone formation; there has been a good deal of skepticism as to whether "acidosis" is of the same nature in dogs, or, indeed, even as to its occurrence. If such doubts be well grounded, much experimental work will have to be revised.

Minkowski[79] found that ketonuria does not *always* follow total pancreatectomy in dogs, and hence interpreted ketonuria as a complication of diabetes. Brugsch and Bamberg[80] held that "acidosis" furnishes the essential difference between canine and human diabetes, extreme acidosis never occurring in depancreatized dogs, which invariably die of inanition rather than in coma. They attach great importance to this postulate, believing that a severe diabetes with pronounced acidosis is probably not a pancreatic diabetes.

Allard[81] and Minkowski[82] opposed this view, proving that in dogs totally depancreatized, acidosis is not rare. Five of Minkowski's dogs

excreted large amounts of ketone bodies. Allard cites three cases of marked acetone excretion (from 2 to 3 gm. total acetone in dogs of 8 to 9 kg.), moderate amounts of acetone, diacetic and beta-oxybutyric acid being demonstrated in many depancreatized dogs. Normal adult dogs on starvation show only traces. Both Allard and Minkowski describe cases of probable death in coma. This ketonuria of dogs has been abundantly confirmed.[82] It is constant after total pancreatectomy.[84]

Large amounts of diacetic acid are formed in the surviving livers of depancreatized dogs, perfused with blood.[85]

On the basis of all these findings and of my own observations, I certainly disagree with Allen[86] in his conclusion that "totally depancreatized dogs are generally free from ketonuria." I can affirm absolutely on the basis of my own experiments that *totally* depancreatized dogs *always* develop ketonuria. I can, however, confirm Allen's statement that they often give no ferric chlorid reaction when excreting large amounts of acetone. However, I have at some time or other in every such dog always found aceto-acetic acid by certain of the tests.[87]

With regard to the factors influencing ketonuria in dogs, it occurs in *chronic* diabetes (Sandmeyer[73]) as well as in the total type. It is also generally held that in dogs, ketonuria is *not* increased in starvation, but rather reduced; also is not lessened by utilization of carbohydrates; is augmented by excessive meat feeding, and hence runs parallel to nitrogen excretion.[88]

These statements are in general true for adult dogs, but one should not conclude that dogs would hence be unsuitable for "acidosis" work. It is certain that in dogs, as in man, a lowered carbohydrate intermediate metabolism predisposes to acidosis. Marum's[89] observation that in phloridzin diabetes of dogs acidosis occurs only after exhaustion of the glycogen stores proves this. While dextrose-feeding has but little influence on acidosis in the adult dog, starvation acidosis is readily induced in young ones.[90] Glucose, injected intravenously, diminishes acetonuria in phloridzinized dogs.[91] Hunger acidosis is interpreted as a carbohydrate deficiency acidosis. Adult normal dogs may show traces of acetone in hunger.[92]

Ehrmann[93] found young dogs, when undernourished, to be susceptible to his chemical, ketogenetic factors. He also observed enormous preagonal (inanition) development of ketones in diabetic dogs. Gigon[94] points out that allowance must be made for the fact that the carnivorous dog has accustomed itself to "metabolic tolerance" of carbohydrate withdrawal; also that, in consideration of its body weight, total acetone value of from 0.2 to 0.3 gm. per diem are very high. Von Noorden[95] takes the same view with reference to acquired toler-

ance toward carbohydrate withdrawal, and has *often noted the same phenomenon clinically in human beings.* He also points out that man often shows a high degree of ketonuria, even when fed such large quantities of carbohydrates (from 50 to 100 gm. per diem) as would promptly control starvation acidosis of a non-diabetic.

Again, if a dog be fed for a long period on much bread, and then be put suddenly on pure meat diet, strong acidosis develops. Heavy protein feeding has a ketogenetic influence on man also, even to the point of danger.[96]

We have, then, a marked parallelism between all these phenomena in man and dog, and from these researches and my own observations, I believe there is no basic difference between the acidosis of a diabetic dog and that of man.

B. CHOICE OF TYPE OF DIABETES

The question arises as to the *form* of diabetes most appropriate. As Macleod[97] points out, there is practically but one form of permanent hyperglycemia, and, of special relevance to our problem, only one form of experimental diabetes "which can be considered as analogous with the severer forms of the disease in man," namely, that following total pancreatectomy. It also seems that Leschke's[98] dictum, "In view of the intermittent character of the glycosurias, which arise through partial extirpation of the pancreas, no conclusions can be drawn as to the influence of any medicinal drug on glycosuria," applies equally well to an investigation of the effect of ketonuria. Certainly in view of the fluctuation known to occur in the glycosuria and ketonuria of partial pancreatectomy, the logical *first* phase of such an investigation is on the completely diabetic animal.[99]

C. TECHNIC OF PANCREATECTOMY

Twenty-three extirpations were done essentially by the method used by Minkowski and Witzel,[100] all the later ones by Hédon's technic[101] in two stages, dislocating a lobe of the processus uncinatus amounting to about one-sixth to one-tenth the total volume of the pancreas, to a subcutaneous position, with preservation of the vascular pedicle, and, later, extirpation of this. Hédon[101] is certainly correct in maintaining that failure to obtain the concomitant symptoms — as polyphagia, polyuria, wasting — and, he might have added, the dextrose-nitrogen ratio of 2.8 or above, is certainly due to *incomplete* extirpation. Of course, pyogenic infection will lower the dextrose-nitrogen ratio.

D. METHOD OF APPLICATION OF OPOTHERAPY

All *parenteral* routes have been rejected, in view of the following considerations:

1. The complications attendant on these methods — as constitutional disturbances, with chills, fever, etc. — all inevitably associated with depression of general metabolism, and hence easily giving rise to erroneous deductions and conclusions.

2. The possibility that parenteral, and especially subcutaneous, administration may reproduce, more or less accurately, the toxic syndrome of "acute pancreatic poisoning," thus complicating the interpretation by introducing factors far removed from the physiologic norm, and hence not only having no relation to true opotherapy (which must seek to approximate physiologic conditions), but even tending to obscure any such associated specific action.[102] Lattes[103] believes that activization and passage of the tryptic ferment into the blood are possibly responsible for these sudden metabolic deaths.[104]

3. Perfusions of isolated organs were discarded on the basis of such conclusions as that of Ringer and Fraenkel,[105] who deplore the artificiality of this method and its departure from physiologic conditions. Verzar and Fejer too have given expression to very cogent reasons for mistrusting this method, at least where problems of general metabolism are at stake. The organism as a whole may comport itself quite differently from the isolated organ.[106] Dakin and Dudley[78] also show that such researches as have been already conducted along this line with pancreatic extracts are of doubtful interpretation.

E. GENERAL EXPERIMENTAL PRECAUTIONS

1. All dogs were discarded in which any postoperative suppuration or infection persisted. Any such process may lower glycosuria, and also undoubtedly disturb other factors.[107]

2. The dogs used were females; not very large; especially not deep chested; not fat; weight about 6 to 8 kg.; adult, but not old; free from disease, especially mange and distemper; best of all, animals immune to distemper through previous infection. In one series of nine I used a prophylactic vaccine furnished through the kindness of Dr. James W. Jobling and Dr. Carroll Bull, prepared by isolating the *Bacillus bronchosepticus* (Ferry[108]) from the blood of several actively distempered dogs. Those animals which recovered from the effects of the powerful vaccine were apparently immune. All animals with gastrointestinal disorders were rejected.

3. Before the pancreatectomy the urine was examined at least two days for sugar, etc.

4. Before the total pancreatectomy (or the second stage of the Hédon) the dog was brought into approximate nitrogen equilibrium (metabolic cages).

I soon learned to avoid long preoperative confinement of animals to the cage, and, by the Hédon method, was able to feed the animals

even on the day of the second operation. Preliminary starvation (necessary for the old Witzel technic) interferes with metabolic work.

F. CHEMICAL AND ANALYTICAL METHODS

1. Presence and nature of reducing bodies by Haines or Fehling; polariscope; fermentation; phenylozazones. Quantitative sugar by Bang;[109] later by new Benedict,[110] often controlled by polariscope.

2. Ammonia nitrogen by Folin;[111] ammonia nitrogen plus amino nitrogen by Malfatti.[112] Total nitrogen by Kjeldahl.

3. Aceto-acetic qualitative by ferric chlorid; also Hurtley's test[113] and Ondrejovich.[114] The ferric chlorid was almost invariably negative. Acetone qualitative by Langes'[115] di-nitroprussid.

4. Quantitative "total acetone" by the Messinger-Huppert method;[116] also at times checked up by Neuberg's modification of Messinger's method; but the results tallied closely. I felt justified in using the easier "total acetone," rather than the more difficult beta-oxybutryric acid determination, since Gigon[117] has shown the constant relationship which subsists, *in a given individual,* between excretion of acetone and of beta-oxybutyric acid. Embden and Schmitz' warning[118] to avoid drawing over ammonia or other bodies fixable by iodin was carefully heeded.

5. Hepatic glycogen was only twice determined, and only by the method of Pflüger.[119] This omission was justifiable because (*a*) the dextrose-nitrogen ratios indicated total diabetes; (*b*) after the first ten or fifteen operations the extirpations were with certainty technically *total*; (*c*) even on the assumption that small fragments or accessory pancreases had escaped observation in a few animals, the general tenor of the results is dependent not at all on the presence of a total diabetes. The conclusions are valid for a *severe* or *total* diabetes. Several of the later experiments, indeed, as will be seen, purposely represent incomplete extirpations, with no glycosuria on meat diet.

In the two cases in which hepatic glycogen was determined, the figures showed a practically complete absence of all glycogen. In one (Protocol 5) a 186-gm. liver contained 0.12 per cent., or 0.22 gm. glycogen. In the other (Protocol 6) a 247-gm. liver contained 0.08 per cent., or 0.197 gm. glycogen.

G. GLUCOSE THRESHOLD IN DOGS

The dextrose threshold of *normal* dogs is variable, but in general runs from 3 gm. per kilogram weight (Hofmeister's figures) up to from 11 to 16 gm. per kilogram weight (Pflüger's). Relation to other food taking is important, as when given alone the average tolerance is probably 4 or 5 gm.; when given with other food, 10 gm. or over.[120]

IV. PROTOCOLS

Adult normal dogs show no ketone-excretion on pancreas feeding, or, indeed, on any dietetic regimen. This was verified on several normal controls, observed carefully for many weeks. Thus the "total acetone" was determined on Dog 7 for a period of one month. During this time there were administered two heavy feedings of pancreas, with no rise in the total acetone figure, the latter showing, throughout the month, the usual variation of normal dogs, from 0.002 to 0.01 gm. per diem for animals of 5 to 12 kg. weight. Since immature and adolescent animals were not used in these experiments, only *adult controls* were used.

With regard to the effects of *starvation*, adult dogs show no increase of "total acetone," even on prolonged starvation. Elias and Kolb[92] have already shown that young normal dogs respond to starvation by ketonuria.

Adult, totally diabetic dogs show no appreciable effect of starvation on acidosis, until the starvation has been prolonged to the point of inanition, which means absolute starvation for at least five or six days. This is illustrated by Protocols 1 and 2.

PROTOCOL 1.—Dog 35.—Total Extirpation, June 19, 1913

Date June	Food	Total Acetone gm.	Weight kg.
18-19	400 gm. beef	.012	15.4
19-20	None	.0167	....
20-21	None	.0366	....
21-22	1 liter milk	.078	15.2

PROTOCOL 2.—Dog 31.—Total Extirpation, March 14, 1913

Unable to retain any food after pancreatectomy. Water taken in moderate amounts.

Date March	Total Acetone gm.	Weight kg.
12-13	.0021	4.2
13-14	.0044	...
14-15	.0113	...
15-16	.0521	...
16-17	.0643	...
17-18	.0517	4.0
18-19	.0608	...
19-20	.0710	3.8
20	death (inanition)	

Lüthje[121] also incidentally shows[122] that there is very little starvation acidosis in adult, depancreatized dogs.

Protocols 1 and 2 serve to illustrate another general observation, namely, that after total pancreatectomy the total acetone figures *always* rise moderately, irrespective of feeding or of starvation. The figures for normal dogs vary between 0.002 and 0.01 gm. per diem for dogs of from 5 to 12 kg. weight. After total extirpation these rise to from 0.01 to 0.09 gm. for dogs of this size. The increase is rather gradual

and progressive, and will not go much above 0.09 gm. on mixed diets, or on starvation.

PROTOCOL 3.—TOTAL PANCREATECTOMY (SECOND STAGE) JULY 3, 1913, OF DOG 50, WHICH COULD RETAIN NOTHING BUT WATER UNTIL DEATH

Date July	Total Acetone gm.	Weight kg.
2-3	.002	4.4
3-4	.0078	...
4-5	.009	...
5-6	.038	4.2
6-7	.0309	...
7-8	.077	...
8-9	.472	3.8
9 death		

In the case of Dog 50 (Protocol 3), as occasionally, there was an immense preagonal increase. Preagonal decrease almost to the zero mark was sometimes observed.

We cannot doubt from the observations of Elias and Kolb[92] on young, normal animals that if young, diabetic animals had been used, the diabetic acidosis would have increased under starvation.

Aside from such controls, the general plan of the experiment was to place animals of known weight on diets so chosen as to satisfy calorific requirements, and then to replace, for definite periods, a part or all the protein by isodynamic amounts of pancreas (or liver, etc.), noting the influence on ketone excretion. It soon became apparent that the matter of control diet (that is, the food regimen of the days on which no pancreas was given) was very important, if one were to avoid confusing results and fallacious deductions. Much time and many animals were lost in the slow working out of these considerations. The earlier experiments showed that high protein food of any sort in a diabetic animal exerts a decided ketogenetic influence. Hence the necessity arose of preceding the feeding of pancreas by a diet including some other protein isodynamically the equivalent of the pancreas to be fed. After preliminary essays of a basal mixed diet, it was soon thought best to use a straight protein diet of lean meat. This was suitable for the carnivorous dog, and, in the form of lean, hind shank of beef, possessed the additional advantage of permitting protein and nitrogen content to be easily controlled. Later, dextrose and fat were added to the basal diet in some of the experiments. In general, a moderate excess of protein food constituted the fundamental diet.[128]

It became evident from the earlier experiments in which no quantitative determinations of ketones were made, the intensity of color reactions being relied on, that on a moderately high protein diet of lean beef after total pancreatectomy, ketonuria sometimes developed, but with moderate intensity and rapidity, while the reaction to pancreas feeding was prompt, and marked by extreme development of aceto-

nuria. In Protocol 4, only the qualitative tests were invoked, but these were carefully done, and included, each day, the various modifications of the di-nitro-prussid-alkali test for acetone; and the Gerhardt (ferric chlorid), Hurtley[113] and Ondrejovich[114] (iodin) methods for aceto-acetic acid. On the twelve control days preceding the extirpation there was never a trace of acetone or aceto-acetic acid demonstrable. After the pancreatectomy, on diets varying between beef or dextrose, or beef and dextrose, there were no demonstrable ketones, but on the third and fourth twenty-four-hour periods (postoperative) there developed, following the administration of raw beef pancreas in doses of 30 gm., a positive acetone test, and on the tenth period, following a dose of 125 gm., positive acetone and diacetic reactions. At these two periods the ammonia-amino (Malfatti) jumped up also, as usual in ketonuria, from 0.183 and 0.177 gm. to 0.42 gm. and to 0.438 gm.

Protocol 4 illustrates the same result.

PROTOCOL 4.—Dog 6.—Total Extirpation, Nov. 22, 1912

Date Nov.	Food	Acetone	Diacetic	Weight kg.
20-21	400 gm. lean beef	0	0	13.3
21-22	400 gm. beef 10 gm. dextrose	0	0	....
22-23	No food	0	0	....
23-24	80 gm. beef	0	0	....
24-25	120 gm. beef	0	0	13.2
25-26	200 gm. beef	0	0	....
26-27	200 gm. raw beef *pancreas*	++	+	....
27-28	200 gm. beef	0	0	13.2

Such results, diametrically the opposite of what I had anticipated, since I was not familiar with the literature of pancreatic opotherapy, were so striking that it was decided to investigate the matter by quantitative methods. Protocol 5 is a specimen.[124]

PROTOCOL 5.—Dog 27, Total Extirpation, March 5, 1913

Date March	Food	Total N Intake gm.	Qual. Acetone	Total Acetone gm.	Weight kg.
2-3	400 gm. beef	13.0	0	.0082	7.5
3-4	400 gm. beef	13.0	0	.0098	...
4-5	Starved	0.0	0	.0034	...
5-6	50 gm. beef	1.62	++	.1191	...
6-7	150 gm. beef 20 gm. potato	4.87	++	.1556	7.4
7-8	400 gm. beef 25 gm. dextrose	13.0	++	.1406	...
8-9	140 gm. meat 50 gm. bread	4.80	++	.187	...
9-10	200 gm. beef	6.5	Trace	.097	...
10-11	200 gm. beef	6.5	0	.044	...
11-12	200 gm. fresh pancreas	5.38	+++	1.137	...
12-13	None	0.0	+++	0.495	7.1
13-14	None	0.0	+++	0.297	...
14-15	150 gm. beef	4.87	+	0.1068	7.1

The dextrose-nitrogen ratio confirmed my operative assumption that the pancreatectomy was total.

This table, as many others, illustrates the fact that in total diabetes, ketonuria develops on feeding of high protein in *any* form of meat, but to a much greater extent on raw pancreas. Thus we find total acetones of from 0.1 to 0.4 gm. per diem (for dogs of from 6 to 12 kg.) developing on beef diet, but of 0.3 to 0.6 to 1.0 on dynamogenetically equivalent amounts of raw pancreas. There is considerable individual variation in ketogenetic response; thus one animal may show as great a quantity of total acetone on beef feeding as another does on pancreas; hence it would be misleading to compare the quantitative results (or color reaction) of one dog on pancreas feeding with those of another on muscle feeding. In general, severely or totally diabetic dogs will not develop a *qualitative* acetone (color) reaction after several days' starvation or low diet or on a mixed diet not much above calorific requirements, but will rapidly develop it on high protein, and much more rapidly and intensely on protein-equivalent quantities of raw pancreas.

In some dogs, on moderate or high beef-muscle diet, the qualitative reaction is so marked that the change to pancreas does not render it more intense, inasmuch as it has already a maximum intensity for a color reaction. In such cases, however, the quantitative determinations always show the difference plainly (Protocol 6).

PROTOCOL 6.—Dog 54, Sept. 11, 1913, Second Stage of Hédon Total Pancreatectomy

Date Sept.	Food	Protein N Intake gm.	Qual. Acetone	Total Acetone gm.	Weight kg.
10-11	450 gm. beef	14.61	0	0.01183	4.6
11-12	Starved	0.0	0	0.0230	...
12-13	400 gm. beef	13.0	0	0.0640	...
13-14	350 gm. beef	11.36	0	0.0721	...
14-15	400 gm. raw pancreas	10.76	+++	0.385	4.7
15-16	350 gm. beef	11.36	+++	0.124	...
16-17	400 gm. raw pancreas 100 gm. beef tallow	13.00	+++	0.623	...
17-18	350 gm. beef	11.36	+++	0.2375	...
18-19	350 gm. beef	11.36	+++	0.1942	4.5
19-20	400 gm. pancreas	13.00	+++	0.487	...
20-21	350 gm. beef	11.36	+++	0.3722	...
21-22	Refused food	0.0	+++	0.340	...

Here, after the maximum *qualitative* reaction had appeared after pancreas feeding, it remained essentially unchanged to the end. In general, the aceto-acetic reaction develops only if the acetonuria is intense; this applies especially to the ferric chlorid test, the more deli-

cate Hurtley and Ondrejovich tests being positive with lesser degrees of acetonuria.[123] The development of the aceto-acetic reaction as well as other points is illustrated in Protocol 7.

PROTOCOL 7.—Dog 67, Nov. 28, 1913, Second Stage of Hédon Pancreatectomy

Date Nov.	Food	Protein N Intake gm.	Qual. Acetone	Ferric Chlorid Reaction	Weight kg.
27-28	350 gm. beef	9.74	0.0026	0	9.2
28-29	None	0.0	0.0029	0	...
29-30	350 gm. beef	11.36	0.079	0	...
30-1	350 gm. beef	11.36	0.104	0	...
1-2	350 gm. beef 20 gm. dextrose	11.36	0.0386	0	...
2-3	40 gm. fresh dog pancreas 200 beef 20 dextrose	7.59	0.638	+	9.3
3-4	350 beef 20 dextrose	11.36	0.0603	0	...
4-5	350 beef 20 dextrose	11.36	0.0504	0	...
5-6	80 gm. fresh dog pancreas 300 gm. beef 20 gm. dextrose	11.94	0.542	+	9.0
6-7	Vomited all food	0.0	0.420	+	8.7
7-8	Vomited all food	0.0	0.438	+	...
8-9	Vomited all food	0.0	0.0752	0	8.4
9	Death with edema and coma				

Dog 67 was totally diabetic, its dextrose-nitrogen on the 30th being 3.05. It was on a high protein diet, its weight having been about 9 kg. and its daily lean meat ration from 200 to 350 gm. It illustrates well the action of raw pancreas, and shows that the latter is not cloaked or inhibited by concomitant feeding of dextrose. This and other protocols do, however, seem to indicate that heavy doses of pure dextrose tend to *lessen* acidosis even in dogs. Thus note that on the 30th and 1st the total acetone is 0.104 gm. on beef alone; on the next day it is 0.0386 on the same amount of beef plus 20 gm. sugar. Days 3-4 and 4-5 show the same influence, and I have several times noted this same effect. Compare Protocol 5 above, on days 6 to 9.

Inasmuch as theoretical considerations would lead us to expect more from a hepatic than from a pancreatic organotherapy in diabetes, experiments were also conducted along this line, starting with the expectation that a lowering of dextrose-nitrogen ratio and of ketonuria would result. It was soon found, on the contrary, that glycosuria is not appreciably influenced (except incidentally by the concomitant variations in carbohydrate intake), and that raw liver is, as pancreas, ketogenetic, although not to so high a degree (Protocol 8).

PROTOCOL 8.—Dog 17, Second Stage of Hédon Pancreatectomy, Done Jan. 6, 1913

Date Jan.	Food	Food N. gm.	Total Acetone gm.	Weight kg.
5-6	400 gm. beef	13.0	.0174	8.2
6-7	100 gm. beef	3.25	.058	...
7-8	400 gm. beef	0.13	.092	...
8-9	400 gm. beef *liver*	13.05	.364	...
9-10	400 gm. liver	13.05	.467	8.1
10-11	400 gm. beef	13.0	.302	...
11-12	400 gm. beef	13.0	.1618	...
12-13	400 gm. beef	13.0	.283	...
13-14	300 gm. beef and dextrose 20 gm.	9.74	.124	8.1
14-15	Beef *pancreas* 350 gm., dextrose 20 gm.	9.45	.6023	8.0
15-16	Rejected all food	0.0	.1426	...
16-17	Rejected all food	0.0	.122	7.9
17	Death			

It had seemed possible that beef muscle was less ketogenetic than beef pancreas on account of a possible inhibiting influence of the higher glycogen content of the former, but this explanation was rendered invalid by the results of liver-feeding, for liver possesses a much higher glycogen content than does muscle, yet it has decidedly greater ketogenetic properties. I also ascertained by direct experiment (Dog 53) that the feeding of 1 gm. of pure glycogen concomitantly with the pancreas did not inhibit in the least the ketogenetic action. This was, indeed, to be expected, inasmuch as the only way glycogen could exert such an effect would be by primary splitting to dextrose with absorption, and the protocols amply prove that even large amounts of dextrose (20 gm.) given simultaneously with the pancreas do not exert a marked inhibitory influence on ketone formation. (See excerpt of Protocol 7, above, especially on dates 1 to 6.)

The feeding of fats simultaneously with pancreas gives rise to more marked increase in ketogenesis than that resulting from pancreas alone.

PROTOCOL 9.—Dog 54, Total Pancreatectomy

Date Sept.	Food	Total Acetone gm.	Weight kg.
13-14	400 gm. beef	.064	....
14-15	400 gm. pancreas	.385	4.7
16-17	400 gm. pancreas 100 gm. tallow (beef)	.623	....
19-20	400 gm. pancreas	.487	....

Mosenthal[76] explained the increased ketogenesis, which he observed in his case of severe diabetes on pancreatic opotherapy, as due to increased fat absorption. As proof he cites the fact that a phloridzinized dog (hence with normal absorption) develops ketonuria, while a totally diabetic dog (hence with fat absorption practically nil) shows none. This deduction is fallacious from two points of view: (*a*) In phloridzinized dogs ketonuria occurs, but only after the reserve gly-

cogen depots have been exhausted (Marum[59]). This shows a close relationship between ketogenesis and carbohydrate utilization, but no especial relation between ketogenesis and fat absorption. (*b*) Pancreatic diabetic dogs *do* develop ketosis. In the great majority of these experiments I have avoided fat food, as a complicating factor, and hence I can be positive that increased intestinal absorption of fat is not the only or the main factor in heightened ketonuria after pancreas feeding.

After ketonuria has been once precipitated, especially in a severe form, as by repeated feedings of pancreas, there persists an increased sensitiveness to ketogenetic factors, so that the ketonuria tends to persist, though in lessened intensity, even under a diet non-ketogenetic. This may be due to a permanent, toxic damage (as of the liver) brought about by the first exhibition of pancreas.

Also in several experiments, after a heavy ketonuria had been developed by pancreas feeding, it increased rapidly, the animal was very sick, vomited or refused all food, became comatose, sometimes developed edema, and died three or four days after the development of the intense ketonuria. In such cases the only positive necropsy findings were usually an enlarged liver, bright yellow in color and friable. Microscopically, such livers showed a high degree of fatty degeneration, almost to the point of complete replacement of the liver parenchyma by fat globules. None of the gastric ulcers or duodenal kinks described by Minkowski[126] could be found in these cases of emesis and this is probably a toxic emesis.

COMA DIABETICUM IN DOGS

There is considerable dispute as to the occurrence in dogs and other animals of a true coma diabeticum.[127] Ehrmann[128] discusses the differentiation between true coma and the allied states, and maintains that he obtains true coma in rabbits, by his sodium butyrates. In animals the signs and symptoms are naturally uncertain and difficult of interpretation, but if his objective criteria are valid, I certainly obtained coma in several dogs, and only in ones which had received pancreatic feeding. In those on ordinary carnivorous or mixed diet, death in inanition occurred the second or third week, but no definite coma. In a few there developed, after two or three administrations of pancreas, a narcosis-like sleep, with deep and slow inspirations and short forcible expirations. This came on early (even two or three days after the pancreatectomies) on heavy pancreas feeding, never except on pancreatic feeding, and was accompanied by great ketonuria, but usually (as in most other cases) by preagonal decrease of ketonuria to almost the zero mark. I have already referred to another type of death — the "acute pancreas death."

One must differentiate this terminal syndrome of fatty toxic liver, ketonuria and coma from that of anesthesia liver degeneration. With the exception of the work done in the two months, December, 1912, and January, 1913, a fresh can of highest (anesthetic) purity ether has been opened for each pancreatectomy. But during that period, without the knowledge and contrary to the explicit order of the experimentor, left-over ether, kept in an ordinary bottle and exposed to sunlight, was used. The result was that practically every animal, fourteen in all, died on the fourth or fifth, or sometimes even the second or third days postoperative, displaying malaise, pernicious vomiting, and a comatose condition. The liver was always large and bright yellow. While ignorant of any toxic substances that might develop in ether under these circumstances, I feel assured that the extra burden put on the liver by pancreatectomy must in these cases have proved, in conjunction with some chemical toxins, too much for that organ. Many protocols and experiments demonstrates the slightness of the effect of an anesthesia of *pure* ether on ketogenesis. See, for example, the excerpt from Protocol 2. There is practically no postanesthetic rise in ketonuria in any case.

EFFECT ON GLYCOSURIA

In the earlier experiments it was thought that a reduction of glycosuria and a lowering of the dextrose-nitrogen ratio was observed on pancreatic feeding. But after a few experiments the fallacy became apparent. The food had been suddenly changed from a mixed diet containing considerable carbohydrate to one of pancreas — almost pure protein. Or where this was not the case, the attention had been focused on small chance variations in dextrosuria, incidental to all such experiments. It is certain that no lowering of glycosuria or of the dextrose-nitrogen ratio results from pancreatic feeding in totally, severely or mildly diabetic animals. I do not wish to be understood as questioning the results of Pratt, Spooner and others, with *prolonged feeding* of pancreas in milder types of diabetes.

MILD DIABETES

In several dogs, the size of the transplanted lobe was so regulated that a diabetes accompanied by a slight glycosuria or by a lowered threshold resulted. Thus Dog 74 (Protocol 10) displayed no glycosuria on a diet of meat, or of meat and starchy foods, or on 20 gm. dextrose with meals, but promptly developed glycosuria on 30 gm. dextrose, given with meals.

On pancreas feeding it showed slight increase of acetone, this rising from about 0.002 to 0.008 up to 0.009, 0.01 or even to 0.0974. There was an increase of ammonia-amino during the twelve to twenty-four hours immediately following such feeding, as from 0.67 gm. up to 2. 3.

or even 4.79 gm. The last figure was on feeding of 400 gm. pancreas. The preceding day, on a practically equivalent meal of 400 gm. raw beef, the Malfatti showed 0.863 gm. There was also the usual polyuria observed on pancreas feeding.

PROTOCOL 10.—Excerpt of Protocol of Dog 74, Operated on June 19. (Displayed No Glycosuria on Meat Diet June 20-June 24.)

Date	Diet	Dextrose	Total Acetone gm.	Weight kg.
June				
25	Potato + bread ad lib.	Trace	.0027	8.75
26	400 gm. beef.....	0	.003	
27	Beef 400 gm.; potato ad lib.	0	.0024	8.75
28	300 gm. beef.....	0	.0021	
29	300 gm. beef.....	0	.0080	
30	67 gm. raw dog pancreas ..... 233 gm. beef	Trace	.012	8.8
July				
1	300 gm. beef	0	.0077	
2	250 gm. pancreas (beef)	+ (0.7 per cent. = 2.59 gm.)	.0092	
3	300 gm. beef	0	.0028	
4	300 gm. beef	0	.0026	
5	300 gm. + 5 gm. dextrose (simultaneously)	0	.0014	8.75
6	300 gm. beef	0	.0034	
7	300 gm. beef + 15 gm. dextrose	0	.0030	
8	300 gm. beef	0	.0041	
9	300 gm. beef + 30 gm. dextrose	++ (1.3 per cent. = 4.87 gm.)	.0026	
10	300 gm. beef + 20 gm. dextrose	0	.0046	
11	300 gm. beef	0	.0031	8.7
12	300 gm. beef	0	.0049	
13	300 gm. raw (beef) pancreas	++' (1.26 per cent. = 8.06 gm.)	.072	
14	300 gm. beef	Trace	.0161	
15	300 gm. beef	0	.0072	
16	300 gm. raw beef pancreas	++ (1.12 per cent. = 5.096 gm.	.0974	8.8
17-26	300 to 400 gm. beef per diem	None	*	
27	400 gm. beef + 30 gm. dextrose	++ (3.12 per cent. = 4.99 gm.)	.0044	8.6
28	400 gm. beef	0	.0037	
29	400 gm. raw pancreas..	++ (1.11 per cent. = 4.5 gm.)	.0154	
30	400 gm. beef	++ (2.48 per cent. = 6.2 gm.)	.033	
31	400 gm. beef	++ (1.84 per cent.)	.050	
Aug. 1-5	400 gm. beef per diem..	Always ++	*	

* Not estimated.

Most interesting of all, there developed a *sharp* and *marked glycosuria*, during the twenty-four hours following each pancreas feeding. This was present at no other time, except when over 25 gm. dextrose was given. We have invariably found, in dogs with greatly lowered tolerance but no actual glycosuria on meat diet, that the pancreas opotherapy precipitates glycosuria.

The positive dextrose findings were frequently checked up by polariscope and phenylhydrazin tests.

Similar findings as to the dextrose mobilizing power of pancreas by mouth were obtained on all animals which were mildly diabetic.

It will be noted in Protocol 10 that after the final pancreas feeding there was a persistent glycosuria. This has been observed twice. It seems probable that it falls in the same category as that increased sensitiveness of the diabetic organism to *ketogenetic* factors after repeated pancreatic opotherapy, referred to above. In all likelihood both represent a permanent toxic damage of liver or pancreas.

I am now engaged in determining whether or not the increased glycosurias of pancreatic opotherapy are accompanied by a hyperglycemia.

These influences of pancreas-feeding on ketonuria and glycosuria apply to *fresh, raw* pancreas, and to raw pancreas kept on ice for several (at least four) days, but not to *cooked* pancreas.

Several subsidiary effects of pancreatic opotherapy were noted, but are already generally familiar. Thus the ammonia was increased concomitantly with the ketonuria. Amino-acid excretion was high in severe diabetes. My earlier determinations were unreliable, for I estimated the combined ammonia and amino nitrogen by the Malfatti method, and the ammonia by the Folin method, obtaining the amino nitrogen by subtraction. I was sometimes surprised to find the ammonia figure to be greater than the figure for ammonia plus amino. It was only late in this work that attention was called to the fallacy of using alizarin as an indicator.[129] After this I verified the high amino nitrogen of the totally diabetic animal.[130]

V. INTERPRETATION OF RESULTS

Pancreatic feeding thus gives rise to increased ketonuria. Does that mean to increased ketogenesis? This is a pertinent question, because there is absolute clinical evidence that ketone excretion does not always run parallel to ketone formation.[131] Those who champion the causal relation between ketones and coma diabeticum lay special emphasis on the toxicity of the non-eliminated fractions accumulating in the blood and tissues, this being true whether their toxicity is due

simply to their acidity (Naunyn) or to a specific quality. Again, exhibition of alkalies certainly increases excretion of the bodies.[132]

But there is nothing in the behavior of our animals which would lead us to suspect that ketones are being generated and accumulated before the administration of pancreas, the latter simply increasing their excretion. In such case we should certainly have found at least some moderate increase in ketonuria prior to the opotherapy. In most of the experiments, the pancreas was given at an earlier period after pancreatectomy than one ever sees ketonuria developing on ordinary mixed or even raw beef diet. Moreover, there was no evidence that these dogs were suffering from ketone poisoning (if such an entity exists) prior to opotherapy. Also the toxic symptoms exhibited by the dogs appeared with, and increased in proportion to, the development of ketonuria. And in several of them there was what I interpreted as a real coma, with tremendous amounts of ketone bodies. This parallel development of ketonuria and toxic symptoms puts the burden of proof on those who would contend that the ketones were formed in the tissues early and excreted only under the influence of the pancreatic opotherapy. If one accepts the hypothesis of Embden and Michaud,[133] according to which diacetic and beta-oxybutyric acids are *physiologic*, intermediary products or by-products of the formation of carbohydrates from fat, normally oxidizing to end-products before elimination, but appearing as such in the urine when, on carbohydrate deficiency, fat catabolism oversteps the bounds, then what I have just contended holds true, *mutatis mutandis*, so that even on this doctrine, there is no reason to believe that before opotherapy there were stored up in the tissues such unoxidized ketone bodies.

By what mechanism does pancreas feeding increase ketogenesis? Any attempt to answer this must take into account the factors which influence the production of acetone bodies ordinarily, that is, in the absence of pancreatic opotherapy.

With regard to their ultimate chemical source there is overwhelming accord that they largely arise in the course of intermediary metabolism, from the vitiated splitting of fats.[134] However, one must concede the possible derivation of a portion of the ketones from protein.[135]

This being their ultimate source, what are the contributory or predisposing factors in ketogenesis?

First, and very obviously, *diabetes*. But the limitation of our knowledge in the field of pathophysiology is so great that the word "diabetes" can at present connote but little definite in this sense.

Second, and more concretely, *increased ultilization of fats*.[136] Fats are, for the diabetic organism, ketogenetic.

Third, *deficient utilization of carbohydrates*.[137] Of course, the diabetic organism furnishes the most conspicuous example of func-

tional incapacity for handling carbohydrates. According to the interpretation now most current, there follows on this reduced consumption of sugars a compensatory increase of catabolism of body-fat and protein by way of response to calorific demand, such hypermetabolism then resulting in a false degradation of body fats, and possibly to a lesser extent of proteins (Landergren), ending in ketone formation.[138]

Other minor contributory factors must be mentioned. Thus *young* dogs (and human beings) are more susceptible to the action of any of the influences mentioned, especially carbohydrate deprivation.[92] Also a lessened store of hepatic glycogen predisposes to ketogenesis. This is probably a specific phase under the general factor of lowered carbohydrate utilization; indeed, it *may* be the fundamental mechanism of the latter.[89] The degree of acidosis bears no fixed relation to the degree of glycosuria.[79] In phloridzinized dogs a preservation of the nitrogen equilibrium ensures freedom from acidosis; starvation precipitates it; ingestion of sugar prevents it.[139] What light does this consideration of factors influencing ketogenesis throw on the mechanism by which pancreatic opotherapy increases it?

1. It is probable that feeding of pancreas may augment ketogenesis by determining *increased absorption of fat*. The latter has been proved to be usually greatly impaired when the pancreas is badly diseased or partially extirpated, experimentally or for disease.[140] The evidence, while not unanimous, points strongly to the conclusion that absorption and nutrition are considerably improved by raw pancreas feeding, and this seems to hold for the insufficiency arising from (*a*) incomplete or complete extirpation,[141] (*b*) supposedly complete exclusion of external pancreatic secretion from the intestine,[142] and (*c*) organic pancreatic disease.[143]

The question as to the precise nature of the mechanism through which the pancreas exerts this undeniable influence on fat-absorption is too complex to be analyzed here except cursorily. That influence seems not to be attributable to any known direct effect or character of the external secretion, such as emulsifying power, alkaline content, lipolytic-enzyme content, or to any indirect effect exerted on associated digestive processes, as by controlling the secretion or activity of bile, or the intestinal motility.[144] Lessened digestion of fats is not the solution, since it is certain that the splitting of food fats is but little or not at all impaired in pancreatic insufficiency.[145] Yet there is considerable evidence that pancreatic juice is in some way necessary for absolutely normal fat resorption.[146] As concerns the possible action of *internal* secretion, it is also doubtful whether the pancreas influences fat absorption through its effect on carbohydrate metabolism. Certainly any relation between hyperglycemia and vitiated absorption may be ruled

out.[147] Another allied concept, but of rather vague significance, is that lowered fat absorption is simply a part of the general depressed metabolism of severe diabetes (Allen). Finally, Lombroso has ably championed the view that a special pancreatic hormone exerts a control over the absorption of fat, and possibly its intermediary metabolism.[148] In increase of fat absorption we have a partial explanation of the augmented ketogenesis on pancreas feeding. In those of our experiments in which fats were given concomitantly with pancreas, there was such an increased ketone excretion as to justify the deduction that this may be one etiologic factor, more especially in the mixed diet of the usual diabetic regimen. However, the results cannot be interpreted altogether along this line, because I have, in many experiments, avoided any possible absorption food fats.

2. The degree of *protein absorption* is a possible factor. This is certainly decreased in pancreatic insufficiency and improved on pancreatic feeding.[149] In the removed pancreas (used for opotherapy) trypsinogen is speedily converted into trypsin. Thus, fed pancreas not only has a high protein content per se, but also may help in digestion and absorption of any other food protein. It is certain from the results of the present work that several of the raw protein foods (beef, pancreas, liver) are ketogenetic to the diabetic organism. But whether or not this is a property of the protein, as such, depends on the extent to which proteins are an ultimate chemical source of ketones. There is reason to believe that the rôle is inconsiderable (see above).

3. Almost certainly the ketogenetic properties under discussion are *toxic,* probably owing to autolytic substances which are normally destroyed by the pancreas (detoxicating theory of pancreatic function). This is along the line of Reach's[150] interpretation of the increased glycosuria and hyperglycemia after feeding of raw meats. Such glycogenetic and ketogenetic toxins are probably non-specific for pancreatic tissue, but present in greater quantity in pancreas, or else in a more potent form than in liver or in muscle tissue. They may be conceived of as exerting their ketogenetic influence in many different ways, but most plausibly by deranging the hepatic function.[151]

4. Could the increased ketogenesis be secondary to decreased utilization of carbohydrates? Probably not. For the overwhelming evidence is that opotherapy does not decrease the burning of sugar (see above). Moreover, most of my animals were *totally* diabetic, and hence already oxidizing a minimum of carbohydrates.[152] Of course, those authors certainly go too far who deny any controlling influence of carbohydrate metabolism on ketone-formation in carnivora. Marum's[89] important observation that in phloridzinized dogs acidosis occurs only after the reserve glycogen has been consumed proves this. But it is

undoubtedly true that the correlation between acidosis and carbohydrate non-utilization is not nearly so close in the dog as in man. The adult dog is "accustomed" (von Noorden) to bear carbohydrate deprivation without reacting by acidosis. Allard[51] has specifically shown that the dog does not readily respond to low carbohydrate by acidosis. My experiments repeatedly show that feeding of dextrose in heavy doses does not lessen the acidosis appreciably, once it is developed. Apropos of this possible relation of acidosis to depressed sugar metabolism, it occurred to me near the close of these experiments that the glycogen present in the skeletal muscle might be responsible for the lesser ketogenetic activity of fed muscle, as compared with that of pancreas. But the two experiments on liver-feeding showed that this may be ruled out as a factor, for the liver of a normal dog has a high glycogen content, and yet the ketogenetic response was almost as marked as in the case of pancreas. Pancreas contains only a trace of glycogen. Feeding of glycogen alone gave rise to no increase or decrease of acetone excretion, as was indeed to be anticipated, inasmuch as glycogen, like starch, must be split to disaccharids and monosaccharids before absorption; and we know the latter are not as markedly antiketogenetic in carnivora as in man.

5. Finally, it seems conceivable, although not probable, that, in pancreatic opotherapy, *enzymes* are introduced which stimulate the tendency to ketone formation already present; or expressed more precisely, catalytics, which accelerate the mass-action tendency already inherent in a diabetic organism to vitiated catabolism of fats (perhaps also of proteins), with consequent ketogenesis. I here refer to ferment action on *intermediary* metabolism, for Reach[150] has already excluded the local action of external secretion ferments in increasing fat absorption. There is also the possibility that this opotherapy acts by mobilizing tissue fats, giving rise to increased intermediate metabolism of endogenous fat; the vicious splitting of such fats in the totally diabetic organism would then give rise with certainty to ketones.

VI. SUMMARY

In the severe or total pancreatic diabetes of dogs, ketonuria of sufficient intensity to be demonstrable by the qualitative tests always develops provided the animal survives several days, and is on a diet covering its calorific requirements.

The "total acetone" figures for adult normal dogs of from 5 to 12 kg. weight run about 0.005 to 0.01 gm. per diem.

After total or near total pancreatectomy and on complete starvation (except for water), there is a slight gradual increase to about 0.01 gm. up to 0.09 gm. per diem.

By judicious administration of a low calorie mixed diet after pancreatectomy the total acetone figures may be kept down to about the latter limits.

Heavy protein diets of any sort exert a ketogenetic influence on the diabetic organism. Thus the feeding of an exclusive protein diet of lean beef for several days invariably precipitates a ketonuria appreciable by ordinary qualitative tests, the total acetone going up to 0.1 to even 0.4 gm.

On dynamogenetically equivalent amounts of raw pancreas the total acetone always increases greatly to 0.5 to 0.7 or even over 0.1 gm. per diem, which represents tremendous amounts for dogs; the color reactions have a maximum intensity. Such increases occur on a single feeding of pancreas. The feeding of raw liver is responded to by a greater ketonuria (0.3 to 0.4 gm.) than that following muscle feeding, but not nearly so marked as the reaction after pancreas. These differences were proved to be *not* due to variations in protein content or in glycogen content.

I doubt whether this ketogenetic influence of pancreatic opotherapy is altogether specific. Yet, in view of the consideration that it is so much greater for pancreas than for other representative protein foods we cannot deny the possibility of its being specific.

As to the mechanism of its action, I have shown that it is not referable to increased absorption of protein or of fats, although both these are factors in additional increase of ketogenesis. It may be associated with increased intermediate metabolism of body-fat; I have not attempted to prove this. It is probably a *toxic* action, comparable to the increased glycosuria demonstrated by Reach[150] on pancreas feeding. Doubtless such toxic influences are largely directed toward the hepatic functions.

If views as to the nature of diabetic acidosis be classified into two groups (Allen[158]), namely (*a*) those maintaining that this is a condition *sui generis* (von Noorden and others) and (*b*) those holding it to be due solely to carbohydrate deficiency (Landergren, Forssner, Gigon), then I believe the present experiments tend strongly to show that "acidosis" in dogs may vary independently of the status of carbohydrate ingestion and metabolism.

VII. CONCLUSION

With reference to the practical aspect of pancreatic organotherapy, Allen[158] remarks, "All authorities are agreed upon the failure of pan-

creatic opotherapy in diabetes. The attempts are continued because of the strong theoretical inducements."

On the contrary, after ruling out all doubtful cases and false interpretations, there seem to be a few exceptions to this dictum, namely, cases of diabetes associated with deranged absorption of fats and proteins; and it is only the administration of *unheated* pancreatic emulsion or extracts, including pankreon, by *feeding* which seems to be of avail here. Moreover, both glycosuria and acidosis are increased, and yet, under careful control, this therapy seems to have been, in selected cases, of some benefit.[154]

With reference to their theoretical bearing, these negative results of organotherapy have been repeatedly invoked by the opponents of the doctrine of pancreatic internal secretion (Pflüger, Leschke and others) as effectually negating that hypothesis. But it is metaphysically speaking, one thing not to have proved a doctrine, quite a different thing to have disproved it. We may possibly agree with Hédon's[27] aphorism that the existence of a pancreatic internal secretion will only then have been *demonstrated* when it shall have been possible to check diabetes of a depancreatized dog by some form of pancreatic opotherapy. But we can never consider it *disproved* until the cause of the negative results has been fathomed; as Pflüger remarks, "Negative proofs in themselves have no final force unless the proof shows why they are negative."[155]

Moreover, aside from the philosophical aspect, it is possible to assign several specific reasons for anticipating such negative results. Thus, as Verzar and Fejer[156] aptly remark, "A negative result can be occasioned by various other causes. Thus to mention only one possibility, the amount supplied in this manner to a body from which the pancreas hormone has entirely vanished may be too small to reach a concentration sufficient for the oxidation of sugar."

We have always the undisputed fact staring us in the face that when the pancreas is extirpated a total diabetes is precipitated; and that when a small part of that organ is left in the blood circuit, but otherwise separated as to all organic continuity (even nervous) from the rest of the animal, the latter is yet preserved from diabetes (Lombroso). Biedl[157] is justified in contending that "the entire data on pancreas diabetes . . . testifies decidedly that here an internal secretion of the pancreas is lacking which normally plays a decisive rôle in carbohydrate metabolism."

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100. Witzel: Arch. f. d. ges. Physiol., 1905, cvi, 173.

101. Hédon: Arch. internat. de physiol., 1911, x, 350.

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103. Lattes: Arch. f. path. Anat., 1913, ccxi, 1.

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105. Ringer and Fraenkel: Jour. Biol. Chem., 1914, xvi, 569.

106. Verzar and Fejer: Biochem. Ztschr., 1913, liii, 143.

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118. Embden and Schmitz: (Footnote 116, p. 914).

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122. For instance, Table 1, p. 501.

123. It is notoriously difficult to obtain nitrogen equilibrium in carnivores unless enormous amounts of protein food are given, since the protein tolerance increases, advancing to higher and higher levels (Lusk, Graham: The Science of Nutrition, Philadelphia, Saunders, 1909, pp. 110, 111).

124. In interpreting the tables given below, it must be remembered that there is no discrepancy between a "total acetone" figure of, say 0.0082 gm., and a *negative* qualitative acetone or diacetic test. For even the very sensitive Reynolds' test reacts only with 0.01 mg. in 1 c.c. water — which is about the equivalent (taking 400 c.c. as an average twenty-four-hour urine for a diabetic dog) to 0.004 gm. for twenty-four hours. All these qualitative tests are less sensitive when applied to *urine*, especially dogs' urine and particularly diabetic dogs' urine, than when applied to an aqueous solution of ketones, because of the high pigmentation of the former. The test used here (Legal-LeNobel-Lange) is not quite so sensitive as Reynolds' (Abderhalden: Handbuch der biochemischen Arbeitsmethoden, 1910, iii, Part 2, pp. 900-913). In general, varying of course with the concentration of the urine, a "total acetone" of below 0.09 gm. per diem will not give a qualitative color reaction to acetone. A diacetic (ferric chlorid) test will usually not be obtained with a "total acetone" much below 0.1 gm. per diem. These figures are for totally diabetic dogs, which usually run from 300 to 700 c.c. urine per diem. They correspond to about a 0.0225 per cent. (or 1:4,500) acetone solution, and to about a 0.025 per cent. (or 1:4,000) aceto-acetic solution. However, my use of the quantitative measurements does away with the necessity of emphasizing qualitative results.

125. Labbé (Rev. de méd., 1912, pp. 257, 374), as also Azémar, cited by him, usually found acetone, but no diacetic acid in diabetic dogs.

126. Minkowski: Arch. f. exper. Path. u. Pharmakol., 1893, xxxi, 182.

127. For litreature see Gigon (Footnote 94).

128. Ehrmann: Berl. klin. Wchschr., 1913, l, 12.

129. Macadam: Jour. Path. and Bacteriol., 1913, xviii, 284.

130. Galambos and Tausz: Ztschr. f. klin. Med., 1913, lxxvii, 14. Loeffler: Ztschr. f. klin. Med., 1913, lxxviii, 483.

131. Magnus-Levy: Arch. f. exper. Path. u. Pharmakol., 1899, xlii; Ergebn. d. inn. Med. u. Kinderh., 1908, i, 352.

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133. Embden and Michaud: Biochem. Ztschr., 1908, xii, 262.

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135. Landergren: Nord. med. Ark., 1910, Part 2, No. 10, cited by Gigon: Ergebn. d. inn. Med. u. Kinderh., 1912, ix, 206. Embden and Engel: Beitr. z. chem. Phys. u. Path., 1907-8, xi, 323.

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137. Biedl: Innere Sekretion, 1913, Ed. 2, Part 2, p. 344. Gigon: Ergebn. d. inn. Med. u. Kinderh., 1912, ix, 206, especially Zur Lehre von der Azidose, pp. 285-299. Magnus-Levy: Ergebn. d. inn. Med. u. Kinderh., 1908, i, 352.

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139. Baer: Arch. f. exper. Path. u. Pharmakol., 1905-1906, liv.

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142. Pratt, Lamson and Marks: Tr. Assn. Am. Phys., 1909, xxiv, 266. Pratt and Spooner: (Footnote 9). Allen: Glycosuria and Diabetes, Boston, 1913, p. 996.

143. Thus Masuyama and Schild: Ztschr. f. phys. u. diät. Therap., 1900, iii, 451. Salomon: Berl. klin. Wchnschr., 1902, xxxix, 45. Meyer, E.: Ztschr. f. exper. Path. u. Therap., 1906, iii, 58. Ehrmann: Ztschr. f. klin. Med., 1909, lxix, 319. With these and many other results, the negative findings of Gross have but little weight.

144. Minkowski: Berl. klin. Wchnschr., 1890, xxvii, 333; Arch. f. exper. Path. u. Pharmakol., 1908, lix, 395. Lombroso: Beitr. z. chem. Phys. u. Path., 1908, xi, 81; Ergebn. d. Physiol. (Ascher-Spiro), 1910, ix, 1, especially p. 11, Sammelreferat. Arch. di fisiol., 1910, viii, 209. Arch. di farm., 1910, ix, 446. Allard: (Footnote 81). Niemann: Ztschr. f. exper. Path. u. Therap., 1909, v, 466.

145. Abelmann: (Footnote 141). Hédon and Ville: Arch de physiol. norm. et path., 1897, xix, 606, 662. Gross: Deutsch. Arch. f. klin. Med., 1912, cviii, 106.

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147. Minkowski: Berl. klin. Wchnschr., 1890, xxvii, 333. Lombroso: Beitr. z. chem. Phys. u. Path., 1908, xi, 81.

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150. Reach: Biochem. Ztschr., 1911, xxxiii, 436.

151. Concerning the relation of acidosis to hepatic insufficiency. see: Allard: (Footnote 81). Friedmann and Maase: Med. Klin., 1910, xxxi, 445. Blum: München. med. Wchnschr., 1910, lvii, 682. Neubauer: (Footnote 90).

152. A totally depancreatized dog has lost all ability to oxidize dextrose four days after the operation (Verzar and Fejer, Footnote 84).

153. Allen: Glycosuria and Diabetes, Boston, 1913.

154. Compare Mosenthal, E. Myer, Wegele. Allen himself admits this further on (Glycosuria and Diabetes, p. 815).

155. Pflüger: Arch. f. d. ges. Physiol., 1907, cxviii, 285: "Negative Beweise aber haben an sich keine entscheidende Kraft, wenn nicht der Beweis vorliegt, *warum* sie negativ sind."

156. "Ein negativer Erfolg kann durch verschiedene andere Gründe bedingt sein. So kann — um nur eine Möglichkeit zu erwähnen — die dem genzen Körper aus dem das Pankreas-Hormon volkommen verschwunden ist auf diese Weise zugeführte Menge immer noch zu klein sein, um eine zu Zuckerverbrennung genügende Konzentration zu erreichen." Pflüger, too, has admitted this (Arch. f. d. ges. Physiol., 1907, cxviii, 267).

157. Biedl: Innere Sekretion, 1913, Ed. 2, ii, 359: "Das gesamte Tatsachenmaterial über Pankreasdiabetes . . . spricht wohl entschieden dafür, dass hier bei ein inneres Sekret des Pankreas in Wegfall gekommen ist, welches de norma im Kohlenhydratstoffwechsel des Organismus eine ausschlaggebende Rolle spielt."

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STUDIES ON THE PATHOLOGICAL PHYSIOLOGY OF THE HEART

I. THE INTRA-AURICULAR, INTRAVENTRICULAR AND AORTIC PRESSURE CURVES IN AURICULAR FIBRILLATIONS *

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INTRODUCTION: THE VALIDITY OF EXPERIMENTAL RESULTS IN THE INTERPRETATION OF CARDIAC AFFECTIONS

The experimental investigator who, within the span of at most a few hours, seeks to reproduce in animals the cardiac affections which Nature pleases to produce in man in a slow and gradual fashion, runs the risk of bringing about conditions which may not be comparable to those actually existing in diseased individuals. Thus, the sudden tearing of a valve may produce a reaction in experimental animals that is more serious than a similar insufficiency, the gradual development of which is accompanied by compensatory phenomena. It becomes a part of the experimental problem, therefore, not only to elucidate the dynamic effects of a certain pathological change, but also to determine, as completely as possible, the influence that secondary accompaniments to such a condition have on the primary affection.

Moreover, the hearts of animals on which experimental work is carried on are necessarily depressed by operation as well as anesthetic. Even if the anesthetic is wisely chosen and cautiously administered, shock and hemorrhage being reduced to a minimum, the very acts of opening the chest, instituting artificial respiration and removing the pericardium all operate to alter the pressure relations in the heart and large vessels so that the circulation can no longer be regarded as normal. Emphasis may, therefore, be laid on the fact that, in this series of investigations, the effort has been made to have, previous to the production of any pathological disturbance, an "effective auricular pressure" and an arterial pressure as nearly normal as possible. This was accomplished by giving the animal a very mild artificial respiration which caused an accumulation of carbon dioxid in the blood. Furthermore, the pericardium was retained in normal position in these experiments. If this procedure failed to restore normal pressure relations, an infusion of a saline containing 0.2 per cent. dextrose and a $1:10^9$ concentration

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* From the Department of Physiology, Cornell University Medical College.
* The first of a series of experimental and clinical investigations of pathological cardiac conditions made by means of optically recording instruments.

of epinephrin was allowed to enter the external vein very slowly but continuously.

A third difficulty in studying accurately the pressure changes during cardiac disturbances has recently been eliminated. It appears from the critical analysis of the static and dynamic requirements of recording apparatus by Frank[1] that, until recently, physiologists have not been supplied with apparatus which could accurately follow pressure changes in the cardiovascular system. The records obtained were but distorted images of what actually occurred. This unrecognized difficulty has

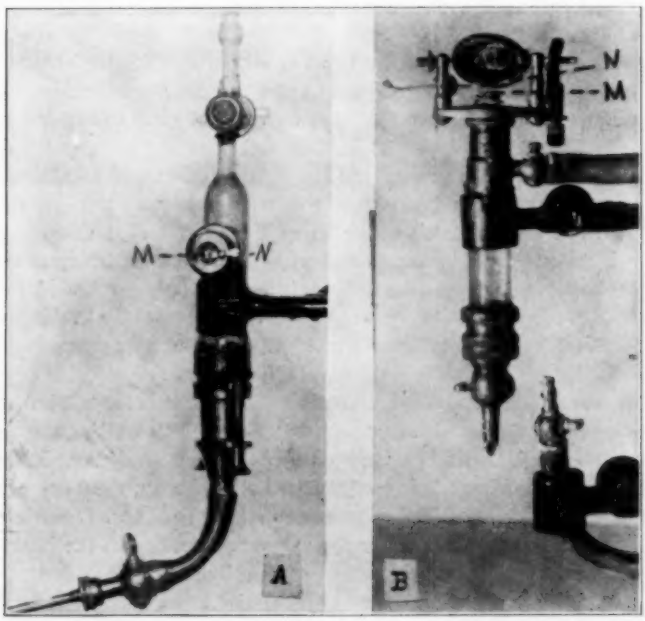

Fig. 1.—Two optically recording manometers: *A*, manometer for auricular, venous or arterial pressures; *B*, manometer for intraventricular pressures; *M*, movable mirror; *N*, calibrating mirror.

given a false feeling of finality in regard to data concerning phenomena involved in the normal as well as the pathological physiology of the circulation. Fortunately, however, it is now possible, on the principles worked out by Frank, to construct optically recording manometers whose efficiency exceeds the demands on them. Only such instruments have been utilized in these researches.

1. Frank: Ztschr. f. Biol., 1903, xliv, 445; 1908, L, 309; 1910, liii, 429, 545; 1911, lv, 547.

THE OPTICALLY RECORDING APPARATUS

1. *Manometers.*—The two types of optically recording manometers are shown in Figure 1. The instrument *B*, used to study intraventricular pressure, has been described in detail,[2] while the instrument *A*, used to study the venous, auricular and arterial pressure, resembles, in principle, another instrument which has also been described,[3] but differs in that it terminates below in a metal cannula which can be rotated and bent at different angles very much as the metal portion of Frank's spiegel-manometer.

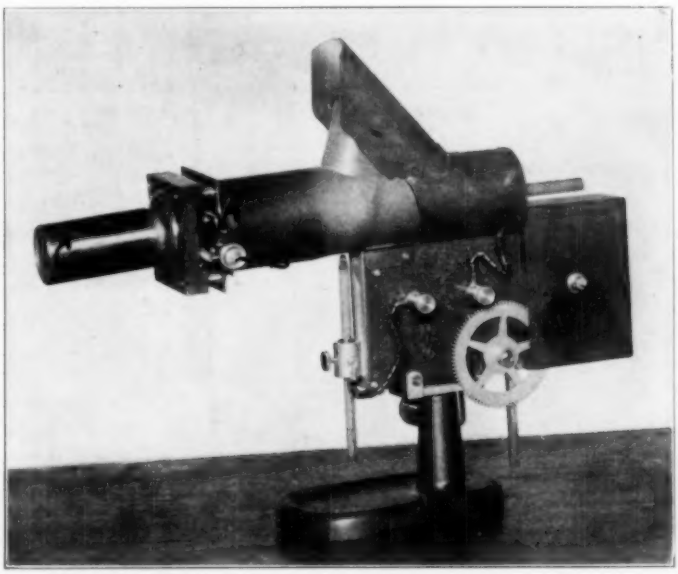

Fig. 2.—Arc light for producing a band of light of variable width. Description in text.

2. *Source of Illumination.*—A small 5-ampere lamp (E. Leitz & Co.), the carbons of which are automatically advanced by clockwork, provides a light of constant intensity (Fig. 2). The rays rendered parallel by a lens at the end of a light-proof hood at *A* pass through a slit the width of which can be regulated through a movable parallelogram system operated by a screw at *B*. By means of this system it is possible to adapt the width of the band to the extent of the excursion, a convenience appreciated when records of very different amplitude

2. Wiggers: Am. Jour. Physiol., 1914, xxxiii, 385.
3. Wiggers: Am. Jour. Physiol., 1914, xxxiii, 8.

need to be recorded.[4] The band of light is focused by a lens *C* on the small mirror of the instrument and reflected as a band of light to the photographic kymograph.

3. *Photokymograph.*—Instruments for obtaining long records have been devised by Edelman[5] and Frank.[6] Some personal experience with both of these photokymographs has led to a selection from each of them of features which, for my purpose, were most desirable, and to their incorporation with certain other features in a new photokymograph (Fig. 3). The fundamental mechanism used by Edelman to propel the paper is retained, except that the camera stands vertically

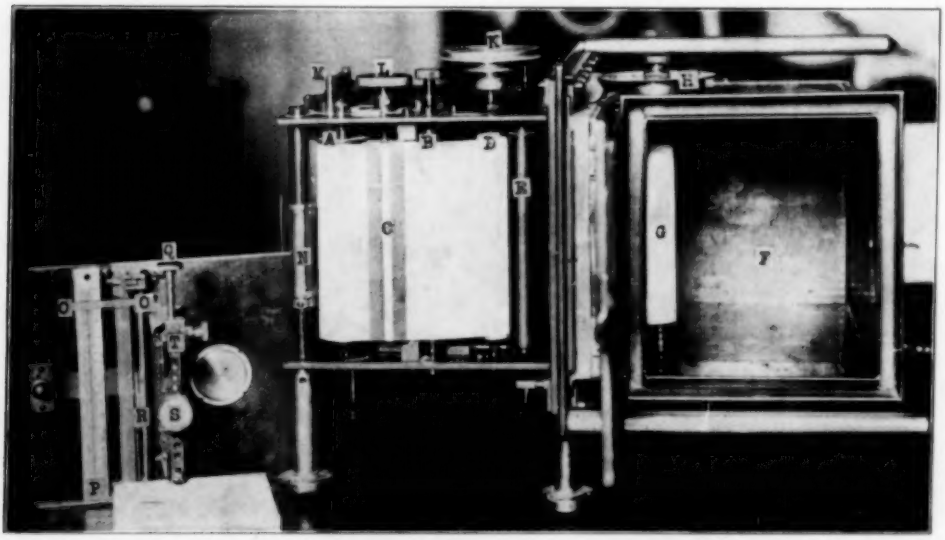

Fig. 3.—Photokymograph showing internal mechanism when front is removed and door of box *F* open. Description in text.

and all rollers move on conical pivots. The paper, 11.8 cm. wide, is fed from a roll 30 meters long and guided by two rollers, *A* and *B*, through a slot *C* and then made to pass between two rubber rollers *D* and *E*. The rubber roller *A* is moved at a definite speed by belting the pulley *K* with a motor and reducing gear. By rotating the knob *L* the roller *E* is pressed against the roller *D* and the paper is drawn

4. For a discussion of this question see Garten: Tigerstedt's Handbuch der physiologischen Methodik, 1911, i, 100.

5. Edelman: Description in catalogue of Edelman Company, Munich.

6. Frank: Reported by Garten: Tigerstedt's Handbuch der physiologischen Methodik, i, 107.

through as by a wringer and passed through a slot into the box *F*. Here it is wound on a roller *G* by a spring attachment *H* as fast as it is fed into this box. This arrangement enables one to dispense with the enormous box of the Edelman apparatus, and is much simpler in construction than the complicated winding gear of Frank's apparatus. At *M* a meter indicating the amount of paper rolled off is introduced. This meter is actuated as follows: The roller *A* is 10 cm. in circumference. As the paper passes over the roller it is maintained in perfect contact by a smaller roller and weak spring at *N*. During every revolution of roller *A* (which occurs each time that 10 cm. of paper has passed) a single tooth at its top engages in one of ten teeth of a sprocket wheel on which a pointer indicates the number of centimeters on a dial. This sprocket likewise engages in a similar manner during every revolution with one of ten teeth of a second sprocket and its pointer indicates the number of meters on a second dial. In turning the knob *L*, the shutter is opened a short interval after the paper has begun to move. The band of light reflected from the mirror crosses the front of the camera as at *O-O'*. At *P* is a scale on which the band can be focused and the extent of its movement determined. A vertical section of this band of light is focused as a line on the paper at *C* by the cylindrical lens *R* on which a scale of 2 mm. is etched. As in Frank's photokymograph, a metal shade (*Y*, Fig. 4) prevents the light of an ordinary room from affecting the film unless the camera is faced toward a window.

Instead of photographing on the paper the numbers of experiments or date which are visible only after development, it is found more desirable when long records are taken, to punch into the paper a set of perforations corresponding in number to the number of the observation or experiment. This is accomplished by the device shown at *T* (Fig. 3), consisting (as shown in Figure 4 in its more lateral view) of a row of ten pointed rods (*X*), any number of which can be entered through the front of the camera by pushing the knob *S*. The rod *Q* controls the number of rods pushed in.

After the termination of an experiment, the paper is cut off by a knife pushed in from behind, which also closes the camera. The slit in the box *F* is likewise closed by pushing in a slide. The entire box containing the roll of exposed bromid paper is removed to a dark room where, with the guidance of the perforations, the roll can be cut into strips convenient for development. I am indebted to the laboratory mechanic, Mr. James Evenden, not only for working out many details of the kymograph, but for many new suggestions in the process of construction.

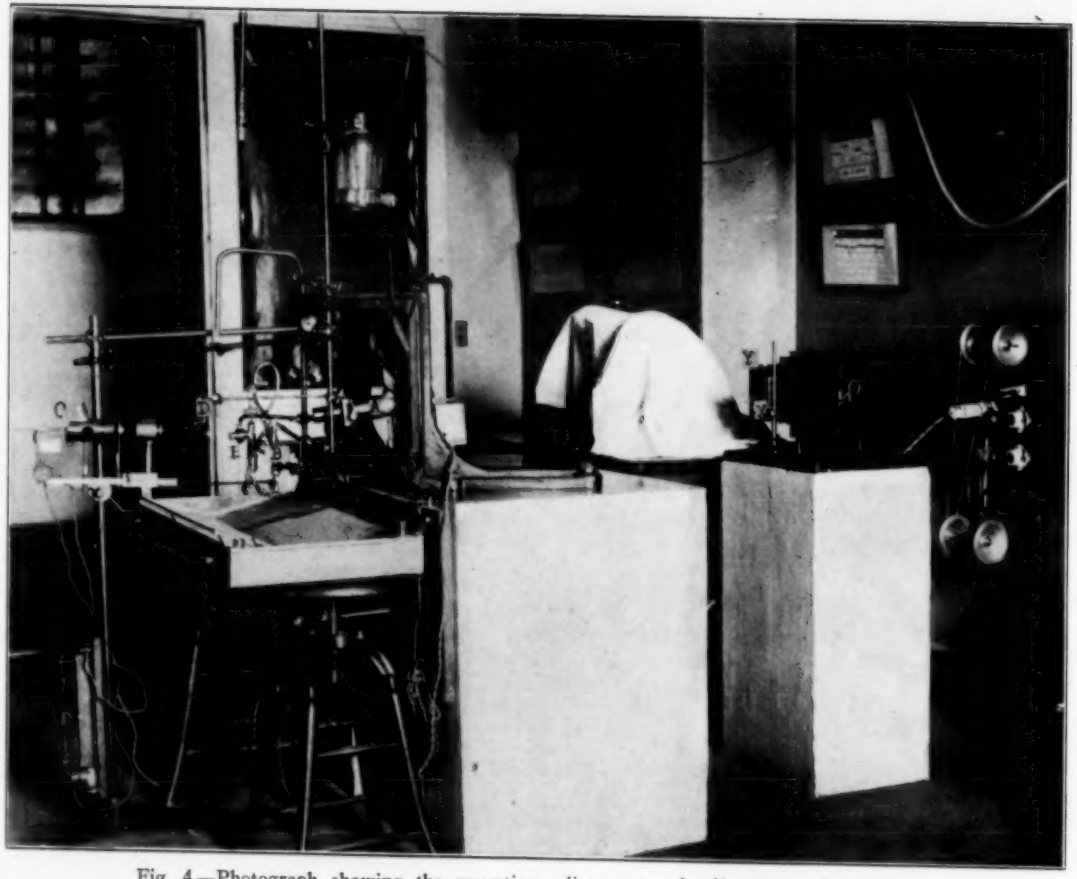

Fig. 4.—Photograph showing the mounting, alinement and adjustment of apparatus.

4. *Mounting and Alinement of Apparatus.*—The main features of the mounted apparatus and its relation to the animal board are evident without further description from the photograph of Figure 4. The band of light from the lamp *A*, set on the cement pillar, is focused on the small mirror of the upright manometer *B* and reflected to the photokymograph which is mounted on a separate pillar. The angle between incident and reflected rays is kept as small as possible. The band of light generated by the lamp *C*, mounted on an iron support clamped to the fixtures of the cement pillar, is focused on the mirror of manometer *E*, whence it is reflected through a small angle to the movable mirror *D*, and so a second time reflected to the optical camera. Since the mirrors of these optical manometers could not be placed exactly in the same vertical plane as the axis of the cylindrical lens, the section of the light bands entering the camera would be brought to a focus at slightly different places on the paper; hence it was necessary when accurate time relations had to be established to expose the paper briefly in the kymograph while stationary. As a rule, the correction was less than 1 mm. and for many purposes could be ignored.

THE NORMAL PRESSURE CURVES AND THEIR TIME RELATIONS

The normal pressure curves in the auricle, ventricle and carotid have been studied by optical manometers by Frank, Straub, Piper, Tigerstedt and myself. Although slight discrepancies exist in the curves obtained, it is possible to express the relations diagrammatically as judged by the combined work of all these investigators.[7]

Aortic Pressure (Plot I, Fig. 5).—Following the description given by Frank, the aortic pressure curve shows a more or less pronounced auricular wave (1, 2, 3), a preliminary vibration (3, 4, 5) synchronous with the isometric period of ventricular contraction, the primary shock (5, 6) due to the sudden ejection of blood with the arteries; the systolic summit reached at 7, the slow fall terminating in the incisure at 8 which marks the end of systole. After this the pressure slowly falls in diastole.

Intraventricular Pressure.—The curve in the two chambers does not differ in its essential features, although the top of the left ventricular curve (Plot II) is broader, that of the right (Plot III) being more rounded or even peaked. The auricular contraction causes a wave (1, 2, 3), which is followed, after several confused vibrations by a rise (3-5) during which the semilunar as well as the auriculoventricular valves are closed, and hence the heart contracts isometrically. After the opening of the valves, the rise continues for a brief interval

7. For reference see Wiggers: Am. Jour. Physiol., 1914, xxxiii, 382.

and the intraventricular pressure responds by a slight though much damped oscillation to the primary rise 5, present in the arterial system. During the ejection period the contour corresponds to the top of the arterial curve since ventricle and arteries form a common cavity. The pressure continues to rise, and late in systole, reaches a summit (7), from which it gradually recedes to 8, where the beginning of relaxation causes a sharp drop of pressure to the base line. In the right ventricle (Plot III) the summit (7) is sooner reached and a more marked fall occurs during the ejection period to 8.

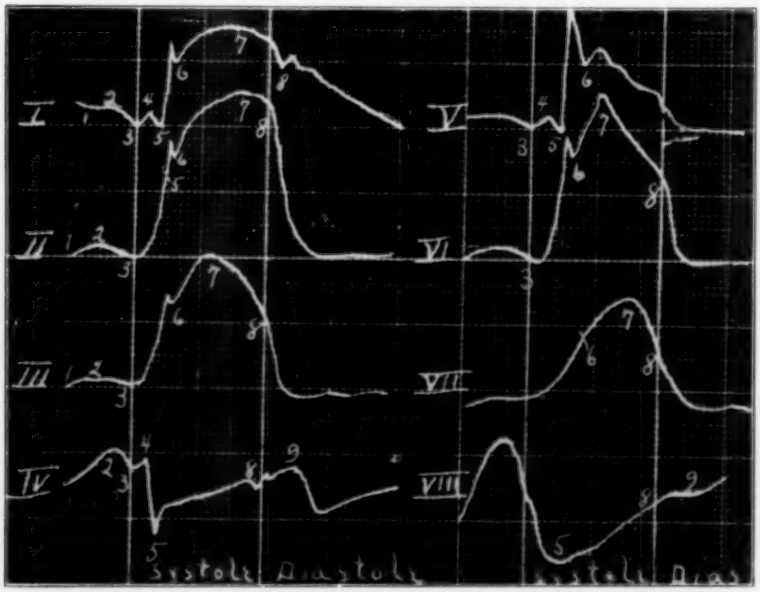

Fig. 5.—Plot showing semischematically the details of the pressure curves as determined by optically recording manometers: I, normal aortic pressure; II, normal left ventricular pressure; III, normal right ventricular pressure; IV, normal right auricular pressure; V, aortic pressure with low resistance; VI, left ventricular pressure with low resistance; VII, right ventricular pressure, low venous pressure; VIII, right auricular pressure, high venous pressure.

Intra-Auricular Pressures.—There is no material difference in the pressure waves of the two auricles (Plot IV, Fig. 5). Auricular systole causes the chief rise (1, 2) and diastole the first fall (2, 3). At the beginning of ventricular systole a short positive rise followed by a rapid negative drop of pressure occurs (3, 4, 5). It remains a question whether this represents more than a vibration of the auriculoven-

tricular valves, or whether, as is usually supposed, first a bulging of the auriculoventricular septum and later a downward movement occurs. Sometimes only a positive wave (3-4) occurs, at other times only the negative wave is present. Often no wave or oscillation of any kind appears. The factors that determine these variations are not established. During ventricular systole the pressure in the auricle rises because of a stasis. This rise continues unmarred except by an occasional vibration synchronous with the semilunar closure (8) until early diastole, when the auriculoventricular valves open and the auricular pressure falls. This does not occur until the ventricular pressure is very low (9).

Atypical Curves.—It may be pointed out that such typical curves are not uniformly obtained; ***in fact, they are never obtained unless special precautions are taken to counteract the deleterious influences of anesthetic and operative procedures.*** The chief variations encountered are due, in the aortic curve, to a low diastolic pressure; in the auricular curve, to a low or high effective venous pressure, and in the ventricular curves to the resultants of both of these influences. A low diastolic pressure in the arteries (Plot V) causes the primary oscillation 5-6 to become greater and more pronounced, while the systolic summit at 7 is much lower and the incisure occurs nearer to the diastolic pressure level. The left intraventricular pressure curve in such cases (Plot VI) resembles more the pressure curve in the right ventricle or acquires a peaked appearance because its maximum is rapidly reached.

The auricular pressure determines the gradient of the isometric rise, the curves becoming steeper with each increase in pressure. The contour of the ejection curve is also secondarily modified, as described in a recent contribution. A curve showing the type of intraventricular pressure curve when the venous pressure is low is shown in Plot VII.

In the auricular curve the chief differences consist in the entire absence of the systolic vibrations already mentioned and a more rapid and complete rise of pressure during systole (Plot VIII). Occasionally, the pressure fails to fall materially at the opening of the tricuspid valves. The size of the auricular wave varies exceedingly.

THE PRESSURE CURVES IN AURICULAR FIBRILLATION

The characteristic pressure variations produced during experimental auricular fibrillation are best analyzed by reference to a number of records taken from seven experiments on the subject.

In Figure 6 are shown simultaneous records of the subclavian (upper) and left auricular pressures (lower). The short record at *A* indicates the nature of the normal pressure curve just before the onset of fibrillation. In Record B is shown by contrast the effect of auricular

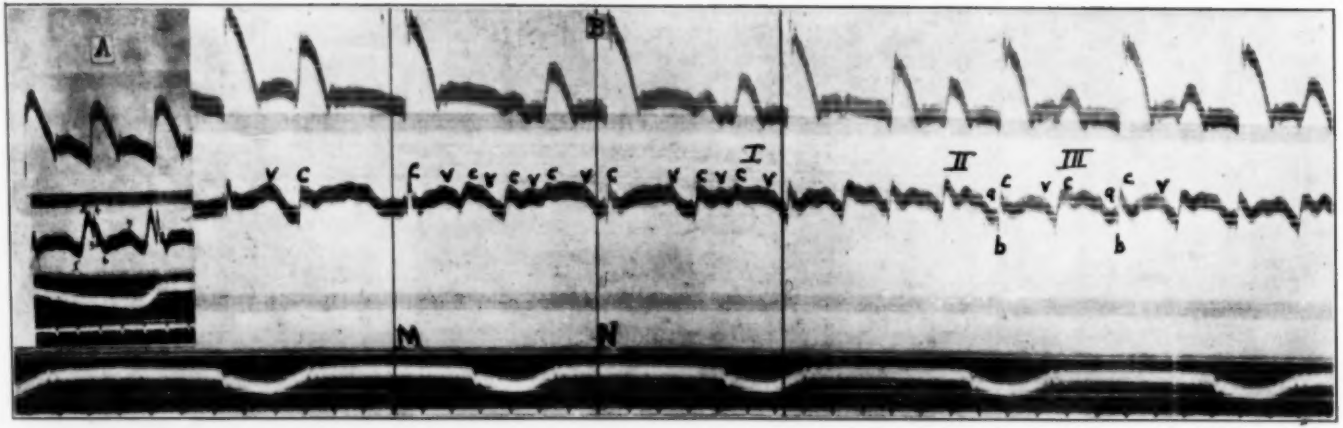

Fig. 6.—Synchronous records of the subclavian pressure (upper record) and the right auricular pressure (middle record). Lower record, artificial respiration. Record A: Normal pressures; 1, 2, 3, auricular wave; 3, 4, 5, early systolic fall of pressure. Record B: Pressure after auricular fibrillation, showing absence of auricular waves, retention of characteristic vibrations, *a*, *b*, *c*, during strong systoles of ventricle. Various other types of waves in weak systoles — described in text.

fibrillation. In the intra-auricular curve there is an entire absence of an auricular wave such as is shown at 1, 2, 3 in the normal curve (*A*). Strong ventricular contractions are initiated by a sharp negative depression (*a-b*) followed by a sharp positive wave (*b-c*) as in the normal pulse. Weaker ventricular systoles, such as are marked I, II, III in the subclavian pulse, cause no such sharp valvular vibrations. They may, as in Wave I, produce merely a ripple in the intra-auricular curve, or after a negative depression (*a-b*) cause a wave which is either sharp as in Wave II or rounded as in Wave III.

During diastole the pressure falls at V, which to judge from the interval after the closure of the semilunars is due, as in the normal pulse, to the opening of the tricuspid valves. In addition to the early systolic oscillations (*a, b, c,*) and the diastolic fall (*v*), there occur other waves of shorter duration. These waves were obtained in experiments in which careful observation failed to reveal any coordinated auricular contraction, and hence they cannot be attributed to attempts at coordinated auricular contractions. There is also no proof that the resultant effect of fibrillary contractions can create wavelets of as long duration as these. When, at the end of experiments, the ventricle has entirely stopped and the still beating auricles are thrown in fibrillation, no waves are produced in the auricular pressure curves. It seems probable, therefore, that they are related to ventricular events not recorded in the arterial waves. Evidence that this is the case is presented later on in the paper. According to this interpretation, the period between the lines *M N* contains not two ventricular systoles as indicated by the subclavian pulse, but probably four systoles, each of which causes a *c-v* wave-group in the auricular pressure curve.

The pressure changes which occur within the left ventricle during auricular fibrillation are shown in Figure 7, synchronous with the subclavian pressure curves. The isometric period (*Anspannungszeit*), as shown in Wave 2, extends from *A* to *B*, the ejection period from *B* to *C*. It is evident that systoles varying greatly in strength occur without definite order during auricular fibrillation. The differences in the systoles of different strength manifest themselves in the gradient of the upstroke, in the contour of the ejection period and in the slope of the relaxation curve.[8] It is obvious that the variations in the gradient of the upstroke and ejection period do not, as in hearts in which a normal rhythm exists, depend on the initial tension,[8] but rather on the interval between its onset and the end of the previous contraction. The waves occurring the shortest interval after systole are smallest and the rise is more gradual. According to this view, the waves num-

8. For further details compare Wiggers: Am. Jour. Physiol., 1914, xxxiii, 382.

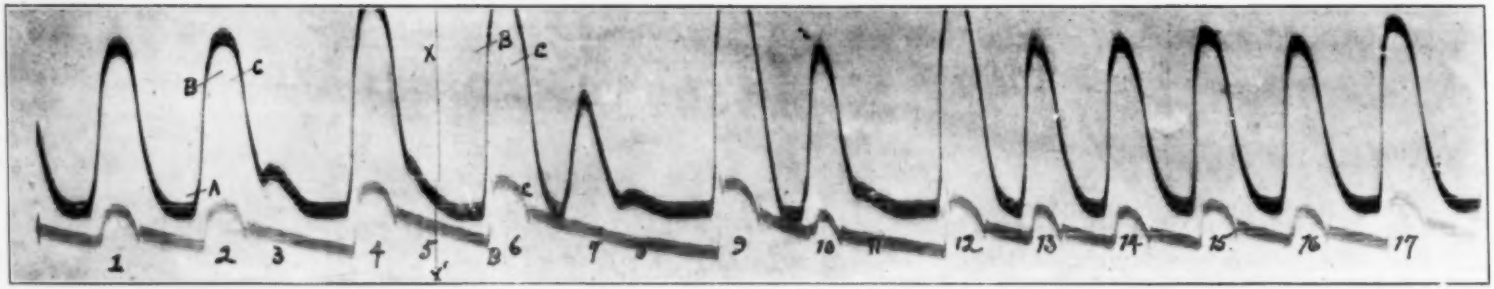

Fig. 7.—Synchronous records of left ventricular (upper) and subclavin pressures (lower) during auricular fibrillation. Description in text.

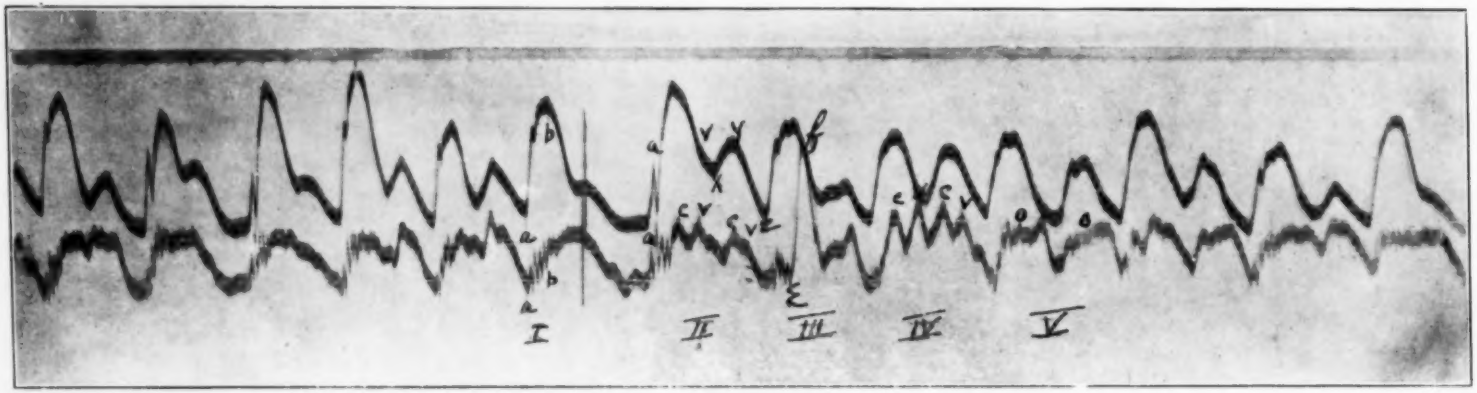

Fig. 8.—Synchronous record of right ventricular and right auricular pressures showing effect of tricuspid regurgitation and effect of weak ventricular systoles on right auricular pressure. Details described in text.

bered 5, 3, 7, 10, 2 and 9 may be arranged as a series. When, however, an extra supply of energy is exhausted by two rapidly recurring systoles, the third wave (as at 8 and 11) may be very small even though a longer interval intervened. The rate of relaxation is directly related to the strength of systole; partly, at least, because, in the weaker systoles, less blood is ejected, partly also, perhaps, because the inherent rate of muscular relaxation is slower, although no direct evidence for this is obtained (cf. e. g., Waves 7, 2 and 6).

The pressure of an aortic pulse curve as well as its shape depends to some extent on the strength of the ventricular systole, but is also governed by the height of the diastolic pressure at the end of the isometric period of cardiac contraction. Thus, while the gradient of the ventricular upstroke and the height of the curve in Waves 10, 13 and 15 are not materially different, the size and shape of the corresponding arterial curves vary extensively. When the semilunar valves fail to open as in Wave 7, the second heart sound fails to occur, while in weaker contractions such as 3, 8 and 11, no sounds can be heard by a stethoscope applied to the dog's heart. This is worthy of note in estimating the "pulse deficit" by auscultating for the heart sounds in auricular fibrillation.

The previous records illustrate a class of cases of auricular fibrillation in which the rhythm given by the ventricle, though irregular, carries on the circulation in a fairly normal fashion. In the experiment shown in Figure 7 the mean pressure in the arteries ranged around 90, and no auricular engorgement or tricuspid regurgitation occurred. Quite a different picture is given, however, by another class of experiments in which the efficiency of the ventricle is impaired. In Figure 8 is shown a section of a record from a case in which the heart was dilated, the venous pressure high and the carotid mean pressure averaged 27 mm. Each group of waves in a heart cycle becomes an interesting study of its own. In Group I, it is shown that the ventricle is still capable of giving strong beats. The intraventricular curve appears fairly normal in spite of some regurgitation, which is made evident in the auricular curve both by the sudden rise of pressure during ventricular systole and by the murmur vibrations created at *a*. In Group II, a vibration occurs in the ventricle, which corresponds exactly in time with the first vibration in the auricle. Little regurgitation probably occurred in this beat. In the auricles are produced a distinct *c* and *v* wave. During the attenuated systole, *x y z* waves corresponding to a *c* rise and a *v* fall are present. Without an intraventricular pressure curve as a guide, these waves might be interpreted as occurring during the diastole of the previous beat or cycle. The third wave group shows after a valvular vibration and at the beginning of

the ejection period a sudden rise *e, f,* apparently indicating that the tricuspid valves were suddenly rendered incompetent during the height of the ejection period and permitted a sharp regurgitation. In the fourth group marked out, two weak ventricular systoles cause no regurgitation, but produce a series of four distinct waves comparable to the *c* and *v* waves explained in Figure 6. Similar ventricular contractions are, however, accompanied by a regurgitation. This occurs in the two waves of Group V, as shown by the immediate and sustained increase of pressure in the auricle as well as by the murmur vibration superimposed at *o*. The chief deviation of the intraventricular pressure curve consists in the slow rate of relaxation which might result from a high degree of tonus or be due to a great accumulation of blood within the ventricle because the average systole occurs with too little vigor. Since the vigor of the systole is inversely related to the frequency of the ventricular contraction, it is apparent that the most efficient circulation will be maintained in auricular fibrillation when the beats are initiated somewhat slowly. Undoubtedly, the well-known beneficial influence due to digitalis in such cases is due to this fact.

SUMMARY

The details of the pressure changes in the auricles, ventricles and aorta during auricular fibrillation were studied by means of optically recording manometers of high vibration frequency.

Intra-Auricular Curve.—In experimental animals the fibrillating contractions in the auricle in themselves produce no intra-auricular pressure waves. The strong ventricular contractions cause a sharp oscillation in the auricle during early systole, while weaker contractions often cause a single rounded wave or a double oscillation similar to *c* and *v* waves of the normal pulse. When, as often happens, two or three weak contractions which produce no pulse in the arterial system follow each other, a series of small waves are created in the auricle (two to each ventricular systole) which gives the erroneous impression that they occur during ventricular diastole.

Intraventricular Pressure Curve. — The intraventricular pressure curves show that the ventricle contracts at a very irregular rate. The height of the pressure and the gradient of the isometric rise before the semilunar valves open is determined largely by the interval between contractions. Hence, whenever the pace is set too rapidly a series of inefficient systoles results which may cause the arterial pressure to fall and the ventricle to dilate. As these weaker contractions often begin before the *a-v* valves are open and are not strong enough to open the semilunar valves, it follows that such contractions may be accompanied

by no audible sound. It is important to realize this clinically in estimating the ventricular rate by auscultation in such cases.

Central Arterial Pulse.—Since the aortic pressure is affected only by those systoles which elevate intraventricular pressure above the arterial diastolic pressure, it follows that the contour and amplitude of the arterial waves depends not only on the strength of ventricular contraction, but on the diastolic pressure as well. Since the venous pulse tracings taken from the supraclavicular region are always complicated by arterial impacts from the central arteries, the failure to recognize this may lead to misinterpretation of the systolic wave groups. The failure to recognize that the arterial pulse amplitude is not a criterion of the strength of the heart-beat in such cases has given rise to the erroneous impression that the strength of the ventricular systoles follows no law, whereas the intraventricular pressure curves show that the vigor of ventricular systole is largely governed by the time relations between contractions.

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THE DISTRIBUTION OF IODIN IN THE CELL FOLLOWING ADMINISTRATION OF ORGANIC IODIN PREPARATIONS *

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In a previous communication[1] results of analyses of tissues were given, showing essential differences in the distribution of iodin in the various constituents of the cell after administration of different iodin preparations. It was believed that a further series of analyses might serve to confirm these results, and throw light on the fate of various organic iodin preparations in the body. It had been previously shown by other investigators that after administration of iodized fats a larger relative proportion of iodin was found in the organs rich in lipoids, such as the brain, spinal cord and liver. Their results had been taken to show that these iodized fats were absorbed in a lipoid soluble form, and were held by the lipoids in the cells. This being the case, these substances should produce a relatively larger amount of iodin in the lipoid fraction, after extraction and separation of the tissue elements according to Koch's method.[2]

In order to establish the results, it was necessary to demonstrate that after mixing various iodin preparations with liver tissue, the tissue originally chosen for the experiments, these substances would follow their solubilities during the extraction process. By a comparison of the results of analyses following mixture of the substances with liver tissue, and analyses of liver following administration of the preparations to live animals by different methods, some idea has been obtained as to the changes in these substances during the process of absorption.

The experiments were carried out in practically the same manner as those previously reported. Extraction of the lipoids, separation of the water-soluble constituents, etc., was done by the method of Koch.

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* From the Laboratory of Pharmacology, University of Oregon, Department of Medicine.

* Investigation supported in part by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

1. McLean, Franklin C.: Organic Iodin Preparations, Their Pharmacology and Therapeutic Value, THE ARCHIVES INT. MED., 1912, x, 505.

2. Koch, W.: Jour. Am. Chem. Soc., 1909, xxxi, 1330.

All iodin determinations were made by the method described by Hunter,[3] with the slight modifications suggested by F. C. Koch.[4]

The following protocols and accompanying tabulation show the results of the experiments made. For the sake of completeness, the results of the four experiments heretofore reported are included, as Series A.

EXPERIMENTS WITH POTASSIUM IODID

EXPERIMENT V.—Feb. 4, 1914, 20 gm. liver mixed with 5.2 mg. potassium iodid and put in alcohol immediately.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.000	00.0
Lipoid	.071	34.1
Water-soluble, alcohol-soluble	.137	65.8
	.208	

EXPERIMENT VI.—Feb. 4, 1914, 20 gm. liver mixed with 5.2 mg. potassium iodid and allowed to stand one hour at room temperature before mixing with alcohol.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.000	00.0
Lipoid	.0761	32.3
Water-soluble, alcohol-soluble	.159	67.6
	.2351	

EXPERIMENT IX.—Rabbit 2,000 gm.
April 6, 1914, 0.3 gm. potassium iodid subcutaneously.
April 7, 0.3 gm. subcutaneously.
April 8, 0.3 gm. subcutaneously, 9:30 a. m.
Killed by bleeding 5 p. m.; weight of liver 54 gm. Liver showed marked fatty changes; 20 gm. of liver taken for analysis.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.000	00.0
Lipoid	.0697	30.5
Water-soluble, alcohol-soluble	.1586	69.4
	.2283	

EXPERIMENT V-A.—Rabbit, 1,600 gm.
July 22, 3 p. m., 0.8 gm. potassium iodid in water by stomach tube.
July 23, 9 a. m., 0.5 gm. potassium iodid in water by stomach tube.
July 23, 10:30 a. m., killed by bleeding from neck. Weight of liver 65.95 gm.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.000	00.0
Lipoid (alcohol-soluble, water-insoluble)	.032	32.0
Alcohol-soluble, water-soluble	.067	67.0
	.099	

3. Hunter: Jour. Biol. Chem., 1910, vii, 321.
4. Koch, F. C.: Jour. Biol. Chem., 1913, xiv, 101.

EXPERIMENTS WITH IODALBIN

EXPERIMENT I.—Feb. 4, 1914, 20 gm. liver mixed with 20 mg. iodalbin, and allowed to stand one hour at room temperature before mixing with alcohol.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.0362	42.1
Lipoid (alcohol-soluble, water-insoluble)	.0179	20.8
Alcohol-soluble, water-soluble	.0317	36.9
	0.858	

EXPERIMENT II.—Feb. 4, 1914, 20 gm. liver mixed with 20 mg. iodalbin and put in alcohol immediately.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.0558	45.1
Lipoid	.0412	33.3
Water-soluble, alcohol-soluble	.0267	21.5
	.1237	

EXPERIMENT VI-A.—Rabbit, 1,600 gm.

July 25, 3 p. m., 2 gm. iodalbin in sodium bicarbonate solution by stomach tube.

July 26, 11:45 a. m., 2 gm. iodalbin in sodium bicarbonate solution by stomach tube.

July 26, 2 p. m., killed by bleeding from neck. Weight of liver, 70.45 gm.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	0.000	00.0
Lipoid (alcohol-soluble, water-insoluble)	.014	24.5
Alcohol-soluble, water-soluble	.043	75.4
	.057	

EXPERIMENTS WITH SAJODIN

EXPERIMENT III.—Feb. 4, 1914, 20 gm. liver mixed with 26 mg. sajodin and put in alcohol immediately.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.000	00.0
Lipoid	.111	89.8
Water-soluble, alcohol-soluble	.0126	10.1
	.1236	

EXPERIMENT IV.—Feb. 4, 1914, 20 gm. liver mixed with 16 mg. sajodin and allowed to stand for one hour at room temperature before mixing with alcohol.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.000	00.0
Lipoid	.072	83.0
Water-soluble, alcohol-soluble	.023	16.9
	.195	

EXPERIMENT II-A—Rabbit, 1,790 gm.

June 24, 0.3 gm. sajodin in olive oil subcutaneously.

June 25, 0.3 gm. sajodin in olive oil subcutaneously.

June 26, 9:30 a. m., 0.5 gm. sajodin in olive oil subcutaneously.
June 26, 1:30 p. m., killed by bleeding from neck. Weight of liver 54.9 gm.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.000	00.0
Lipoid (alcohol-soluble, water-insoluble)	.0106	62.7
Alcohol-soluble, water-soluble	.0063	37.3
	.0169	

EXPERIMENT IV-A.—Rabbit, 1,400 gm.
July 17, 2:10 p. m., 2 gm. sajodin in alcohol by stomach tub .
July 18, 9:30 a. m., 2 gm. sajodin in alcohol by stomach tube.
July 18, 1:30 p. m., killed by bleeding from neck. Weight of liver 49.5 gm.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.010	6.4
Lipoid (alcohol-soluble, water-insoluble)	.082	52.9
Alcohol-soluble, water-soluble	.063	40.6
	.155	

EXPERIMENTS WITH IODIPIN

EXPERIMENT VIII.—Rabbit, 2,950 gm.
Feb. 18, 1914, given 7.3 c.c. iodipin (10 per cent.) subcutaneously.
February 19, 7.3 c.c. subcutaneously.
February 20, 7.3 c.c. subucutaneously.
February 21, 7.3 c.c. subcutaneously, 10 a. m.; 2 p. m., killed by bleeding; weight of liver 100 gm.; 20 gm. of liver taken for analysis.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.000	00.0
Lipoid	.0052	55.9
Water-soluble, alcohol-soluble	.0041	44.0
	.0093	

EXPERIMENT VII.—Rabbit, 3,400 gm.
Feb. 18, 1914, given 8.5 c.c. iodipin (10 per cent.) by stomach tube.
February 19, 8.5 c.c. rectally.
February 20, 8.5 c.c. rectally.
February 21, 8.5 c.c. rectally, 10 a. m.; 2 p. m., killed by bleeding; weight of liver 82 gm.; 20 gm. of liver taken for analysis.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.000	00.0
Lipoid	.0359	77.3
Water-soluble, alcohol-soluble	.0105	22.6
	.0464	

EXPERIMENTS WITH IODIVAL

EXPERIMENT XI.—Rabbit, 2,000 gm.
April 6, 1914, 1 gm. iodival subcutaneously, with alcohol.
April 7, 1 gm. subcutaneously.
April 8, 1 gm. subcutaneously, 9:30 a. m.; 5:30 p. m., killed by bleeding; weight of liver 69 gm.; 20 gm. of liver taken for analysis.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.000	00.0
Lipoid	.0190	81.8
Water-soluble, alcohol-soluble	.0042	18.1
	.0232	

EXPERIMENT XII.—Rabbit, 2,000 gm.
April 6, 1914, 1 gm. iodival subcutaneously, with alcohol.
April 7, 1 gm. subcutaneously.
April 8, 1 gm. subcutaneously, 9:30 a. m.; 5:30 p. m., killed by bleeding; weight of liver 77 gm.

Analysis:	Mg. I per Gram Fresh Tissue	Per Cent. Distribution
Protein residue	.000	00.0
Lipoid	.0126	75.0
Water-soluble, alcohol-soluble	.0042	25.0
	.0168	

TABULATION OF RESULTS OF EXPERIMENTS

		Per Cent. I in Protein Res.	Per Cent. I in Lipoid	Per Cent. I in Water-Soluble, Alcohol-Soluble
	Potassium Iodid:			
V	Mixed with tissue	00.0	34.1	65.8
VI	Mixed with tissue	00.0	32.3	67.6
IX	Subcutaneous	00.0	30.5	69.4
V-A	By stomach	00.0	32.0	67.0
	Iodalbin:			
I	Mixed with tissue	42.1	20.8	36.9
II	Mixed with tissue	45.1	33.3	21.5
VI-A	By stomach	00.0	24.5	75.4
	Sajodin:			
III	Mixed with tissue	00.0	89.8	10.1
IV	Mixed with tissue	00.0	83.0	16.9
II-A	Subcutaneously	00.0	62.7	37.3
IV-A	By stomach	6.4	52.9	40.6
	Iodipin:			
VIII	Subcutaneously	00.0	55.9	44.0
VII	By rectum	00.0	77.3	22.6
	Iodival:			
XI	Subcutaneously	00.0	81.8	18.1
XII	Subcutaneously	00.0	75.0	25.0

It will be seen that the distribution of iodin after potassium iodid is remarkably constant, whether the substance be mixed directly with the tissue, or administered subcutaneously or by the gastro-intestinal tract. The distribution of potassium iodid serves, therefore, as a comparison, as only one-third of the iodin remains with the lipoid fraction during the process of separation of the fractions. The iodin products of fatty acids, however, show a marked increase in the iodin of the lipoid fraction. As is to be expected, this lipoid distribution is the greatest when the substance is mixed directly with the tissue, as no opportunity is offered for the splitting of the combination. In every case of administration of an iodin product of a fatty acid by whatever method there is a decided increase in the relative amount of the iodin of the lipoid fraction. In the case of iodalbin the results were exactly what were to be expected. We had previously shown[1] that much of the iodin of iodalbin was in very loose combination with the protein, while some seemed to be more firmly bound. Extraction by the Koch

method left from 42 to 45 per cent. of the iodin recovered with the protein fraction, the remainder being practically evenly distributed between the two other fractions. When the substance was given by mouth it was apparently all absorbed in a water-soluble form, as none of it was left in the protein residue. This does not, of course, exclude the possibility of some of it being absorbed as an iodin product of an amino-acid.

The foregoing results apparently establish the *Lipotropie* theory of Loeb,[5] and demonstrate beyond a doubt that the iodized fatty acids are absorbed in a lipoid-soluble form and are taken up by the lipoids of the cells. The greater amount of iodin found in the brain and other lipoid-rich tissues by Loeb is thus explained. These iodized fatty acids may, as suggested by Meyer and Gottlieb,[6] circulate in the body as indifferent or inactive substances, be deposited in indifferent locations, and give off free iodin and allow it to act wherever the necessary conditions are present. This also explains the relatively more even excretion of these substances.

CONCLUSIONS

The method used is suitable for comparing the distribution of iodin in the cell after administration of various preparations.

The iodin derivatives of fats and fatty acids are absorbed in a lipoid-soluble form after administration by the gastro-intestinal tract or subcutaneously, and are taken up and held in part by the lipoids of the cells.

Iodalbin loses its identity during the process of absorption, and its iodin appears in the tissues entirely in water- or alcohol-soluble combination.

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5. Loeb: Arch. f. exper. Pathol., 1907, lvi, 310.
6. Meyer and Gottleib: Pharmacologie, Berlin, 1911, p. 358.

STATISTICS OF PELLAGRA IN SPARTANBURG COUNTY, S. C., INCLUDING GEOGRAPHICAL DISTRIBUTION OF THE DISEASE AND ITS RELATION TO RACE, AGE, SEX AND OCCUPATION *

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GEOGRAPHICAL DISTRIBUTION AND RACIAL DISTRIBUTION OF PELLAGRA IN SPARTANBURG COUNTY

The geographical distribution of pellagra in Spartanburg County was considered in detail in the First Progress Report.[1] In general, it was found that morbidity tended to vary directly with congestion of population, although this relationship was markedly disturbed by other factors. The villages of the cotton mills showed the highest morbidity and, when their population was excluded from the figures, the morbidity rate for the city dwellers was about the same as in the neighboring rural population, although somewhat above the morbidity of the rural population of the county as a whole.

The cases of pellagra in Spartanburg County on our records at the end of 1912 included 257 white persons and twenty-five colored (negro and mixed blood), representing a morbidity of 45 per 10,000 whites and 9.5 per 10,000 colored population. This difference was not regarded necessarily as evidence of racial resistance to pellagra on the part of the negro population, but it was thought that industrial conditions might account for it to a large extent.[2]

The field work of 1913 has added to our records of the number of cases in Spartanburg County, bringing the total number of recorded pellagrins up to 847. In 780 of the cases we know the race of the patient and the place in which he lived at the time the disease was recognized. Of these, 680 were white and 100 colored. We have obtained from the Census Bureau of the United States Department of Commerce and Labor, racial statistics of the population of the minor civil divisions of Spartanburg County. Our data enable us, therefore, to inquire into the total morbidity and the racial morbidity from pellagra, not only in the county as a whole, but also in each of these various minor civil divisions, which present differences in industrial and living conditions. The data are presented in Table 1.

* Submitted for publication July 18, 1914.

* From the Division of Tropical Medicine, Department of the Laboratories, New York Post-Graduate Medical School and Hospital.

1. Siler, J. F., and Garrison, P. E.: Am. Jour. Med. Sc., 1913, cxlvi, No. 7, 46; First Progress Report, p. 21.

2. Siler, J. F., and Garrison, P. E.: Am. Jour. Med. Sc., 1913, cxlvi, 51; First Progress Report, p. 26.

The general geographical distribution of the total 780 cases of Table 1 is not significantly different from that shown by the work of the previous year. The highest morbidity was found in the township of Spartanburg and it was somewhat higher (182 per 10,000) in the population of this township outside the city of Spartanburg proper than within the city limits (153 per 10,000). The only other township with a morbidity approaching these figures was Township E, 127 per 10,000, in which a large portion of the population lived in one mill-village. The townships devoted more especially to agriculture showed relatively much lower morbidity rates. It is probable that we have obtained somewhat less complete records of the actual cases existing in the rural districts, but we do not believe that this can account for the marked difference shown. Pellagra in the farming sections showed a distinct tendency to occur in definite foci of limited extent, in which a considerable proportion of the population was affected. In some of these foci the pellagra morbidity approached the figures observed in villages, but on the whole the rural pellagra morbidity was relatively low. We are compelled to believe that the population of the city and of the villages was, in the aggregate, much more subject to pellagra than the population of the country districts. In other words, higher pellagra morbidity was correlated with congestion of the population.

Within the city of Spartanburg, one small ward was practically free from pellagra, namely, Ward 3. The disease was most prevalent in the unsewered wards, 5 and 6, inhabited largely by the families of mill workers. The population of Spartanburg township outside of the city limits also showed a relatively high pellagra morbidity, 182 per 10,000. This population included the inhabitants of several mill-villages, together with a considerable agricultural population.

In all the townships the pellagra morbidity in the white population was considerably greater than in the colored. This was probably due in part to the fact that negroes were not employed in the cotton-mills and relatively few of this race lived in the mill-villages where the disease was most prevalent. It is also probable that our records of negro pellagrins are somewhat less complete than for pellagrins of the white race, although we do not believe that the discrepancy is very great. In general, it may be said that the negro population was more widely scattered than the white, being less than half as numerous in the first place and living for the most part on farms, except the 6,873 in Spartanburg city. In the principal negro section of the city, in Ward 1, the negro population was nearly equal in numbers to the white and in this ward the pellagra morbidity of the two races was approximately equal, 123 and 121 per 10,000. The financial status and general sanitary surroundings of the white people in this ward were on the average much better than for the negroes. The latter race lived in

TABLE 1.—Pellagra Morbidity of Whites and Negroes in the Townships of Spartanburg County

Township	White			Negro			Total		
	Population	Pellagrin	Morbidity per 10,000	Population	Pellagrin	Morbidity per 10,000	Population	Pellagrin	Morbidity per 10,000
A. Campobello	6,587	23	35	2,092	4	19	8,679	27	31
B. Cherokee	4,147	29	70	1,103	1	9	5,250	30	57
C. Beech Springs	8,359	64	77	3,714	3	8	12,073	67	55
D. Spartanburg	21,143	448	212	10,208	72	71	31,354	520	166
E. Pacolet	3,576	62	173	1,921	8	42	5,501	70	127
F. Reidville	4,562	31	68	2,312	10	43	6,874	41	60
G. Walnut Grove	1,128	2	18	1,315	1	8	2,443	3	12
H. Glenn Springs	1,768	2	11	1,176	0	0	2,944	2	7
I. Woodruff	2,982	6	20	1,398	0	0	4,380	6	14
J. Cross Anchor	2,796	13	46	1,171	1	9	3,967	14	35
Total	57,048	680	119	26,410	100	38	83,465	780	93

TABLE 2.—Pellagra Morbidity of Whites and Negroes in the Minor Divisions of Spartanburg Township

Locality	White			Negro			Total		
	Population	Pellagrin	Morbidity per 10,000	Population	Pellagrin	Morbidity per 10,000	Population	Pellagrin	Morbidity per 10,000
Ward 1	2,476	30	121	2,366	29	123	4,842	59	122
Ward 2	1,360	20	145	451	4	89	1,831	24	131
Ward 3	445	1	22	64	0	0	509	1	20
Ward 4	2,450	34	139	1,972	13	66	4,424	47	106
Ward 5	972	32	330	540	4	74	1,513	37	245
Ward 6	2,917	86	295	1,480	14	95	4,397	100	227
Total for city of Spartanburg	10,641	204	192	6,873	64	93	17,517	268	153
Township, excluding the city	10,502	244	232	3,335	8	24	13,837	252	182
Township, total	21,143	448	212	10,208	72	71	31,354	520	166

a wholly unsewered section in poorly constructed dwellings, while many of the white residents of this ward were of the well-to-do class living in well appointed homes. It would appear that the negroes in Spartanburg County have, as a race, been somewhat less subject to the disease than the white population. The difference is not sharp enough to warrant the belief in a distinct racial immunity of negroes, and it doubtless depends to a considerable extent on living conditions.

The smaller number of negroes present and the fairly complete social segregation of the races rendered association of negroes with pellagrins comparatively much less common. The negroes associated hardly at all with the white mill-village population and their closest social relation with the white race was doubtless in the capacity of household servants in the more well-to-do white families.

So many undetermined factors enter into the relationship that it seems unwise at this time to draw any very definite conclusions in regard to racial resistance to pellagra. We are inclined to believe that negroes as a race are only slightly, if at all, less susceptible to pellagra than the white population, and that the racial difference shown in our statistics for Spartanburg County is dependent to a large extent on the influence of other factors.

Synopsis.—The geographical distribution of pellagra in Spartanburg County has been very uneven, the morbidity being much higher in those townships in which the larger centers of population were situated and especially in the industrial communities surrounding the cotton-mills.

The disease was about three times more prevalent in the white population as a whole than in the negroes, but this ratio is not considered to be a true measure of the relative racial resistance to pellagra, but rather as the end-result of the influence of several factors, in part undetermined.

THE DISTRIBUTION OF PELLAGRA ACCORDING TO AGE AND SEX

The distribution of pellagra in respect to age and sex was discussed in the First Progress Report,[3] in which 282 cases then on our records were studied from this standpoint and compared with similar compilations of other published data. At the end of our field work in 1913, we have been able to compile data in regard to the age and sex of 740 cases in Spartanburg County, out of the total 847 cases of which we were able to obtain records, and it seems probable that these 740 cases represent a much larger proportion of all the cases which have actually occurred in this county than has been previously obtained in a unit population of comparable size. Further than this, we possess approximately complete data concerning the age and sex of 257 pellagrins

3. Siler, J. F., and Garrison, P. E.: Am. Jour. Med. Sc., 1913, cxlvi, 44; First Progress Report, p. 31.

living in seven cotton-mill villages, six in Spartanburg County and one in Union County, S. C., which were studied by house-to-house canvass. In these villages we learned the age and sex of 131 pellagra patients in whom the first attack occurred in either 1912 or 1913, and this figure would seem to represent nearly the total number of cases incident there in these two years. Further, the complete census data on the population of these villages are available in our records. The opportunity is thus presented for a more satisfactory study of the distribution of pellagra according to age and sex than has been possible heretofore.

Pellagra Morbidity in Spartanburg County.—Of the 740 available cases in the county, 528 were females and 212 were males, a ratio of nearly 2½ to 1. For the present study it has not seemed worth while to consider the age of these individuals at the time the disease origi-

TABLE 3.—Distribution of Pellagra in Spartanburg County According to Age by Five-Year Periods

Age	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44
Females....	18	27	15	26	68	89	88	68	44
Males.....	22	34	17	10	11	11	8	14	13
Total....	40	61	32	36	79	100	96	82	57

Age	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	Total
Females...	26	21	17	14	4	0	2	1	528
Males.....	15	15	14	16	8	1	1	2	212
Total....	41	36	31	30	12	1	3	3	740

nated, but they have been tabulated according to age at the time the case was recorded in 1912 or 1913. Chart 1 shows the age distribution of the total 740 cases, each individual being indicated by a plus sign in the column corresponding to the year of his age. Chart 2 shows the age distribution of the 528 female pellagrins and Chart 3 the 212 male cases. Certain inaccuracies are obvious in these figures, particularly the tendency for an excessive number of individuals to occur at the ages 25, 30, 35, etc., indicating that the exact age was sometimes not ascertained; and further the excess of individuals in the thirteenth year of age, which is undoubtedly an inaccuracy, probably resulting from evasion of the child-labor law, which has fixed the minimum age of mill-workers at 12 years.

Grouping together the cases in each five-year period, the distribution shown in Table 3 is obtained.

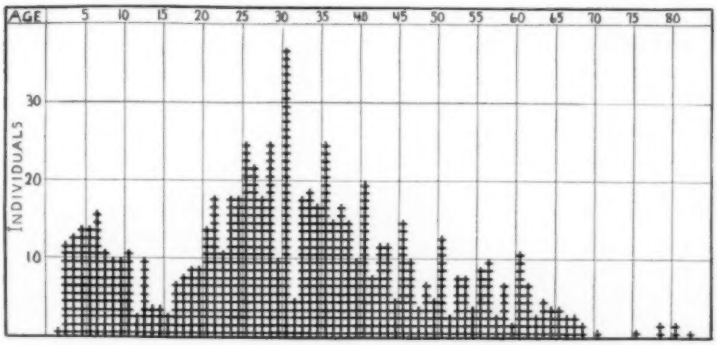

Chart 1.—Distribution of the 740 recorded cases of pellagra in Spartanburg County, according to age at time of record.

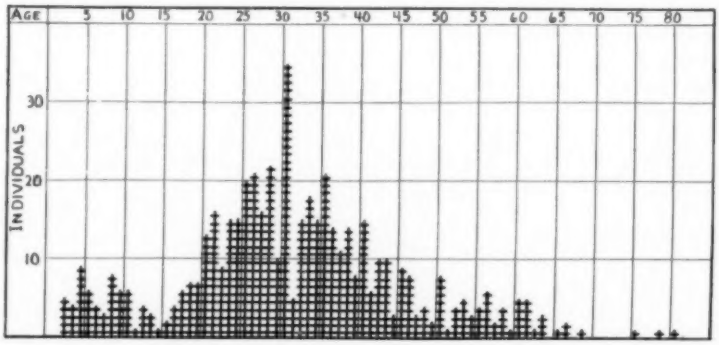

Chart 2.—Distribution of the 528 recorded female pellagrins in Spartanburg County, according to age at time of record.

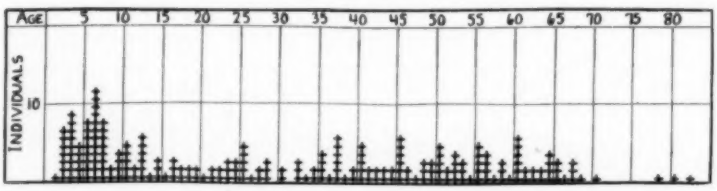

Chart 3.—Distribution of the 212 recorded male pellagrins in Spartanburg County, according to age at the time of record.

The data of Table 3 are shown in graphs in Chart 4.

By comparing the number of recorded pellagrins with the number of individuals in the county according to the United States Census of 1910, it has been possible to obtain an idea of the comparative pellagra morbidity in the age groups shown by the census returns. The data are shown in Table 4.

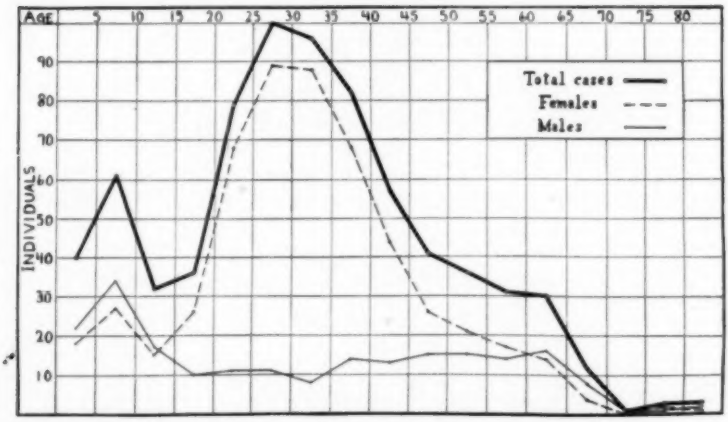

Chart 4.—Distribution of recorded pellagrins in Spartanburg County, according to age at time of record, grouped by five-year periods.

TABLE 4.—COMPARATIVE PELLAGRA MORBIDITY IN SPARTANBURG COUNTY IN THE VARIOUS AGE PERIODS

Age	Females			Males			Total		
	Population	Pellagrins	Morbidity per 10,000	Population	Pellagrins	Morbidity per 10,000	Population	Pellagrins	Morbidity per 10,000
0- 4.....	7,431	18	24	7,763	22	28	15,194	40	26
5- 9.....	4,264	27	62	4,490	34	76	8,854	61	69
10-19.....	10,954	41	37	10,906	27	25	21,860	68	31
20-44.....	13,417	357	267	12,822	57	44	26,239	414	158
Over 44....	5,509	85	154	5,652	72	127	11,161	157	141
Total....	41,675	528	127	41,633	212	51	83,308	740	89

The data of Table 4 are presented in graphic form in Chart 5. Unfortunately, it is possible to locate only five points on each of these curves, because census data for smaller groups of the population are not available.

The general relationships shown in these tables and figures are not significantly different from those shown in the First Progress Report,[4] although, of course, the number of cases of pellagra here considered is much larger and the indicated morbidity rate[5] correspondingly higher. In children the disease was about equally prevalent in the two sexes, the males showing a slight excess. In children under the age of 2

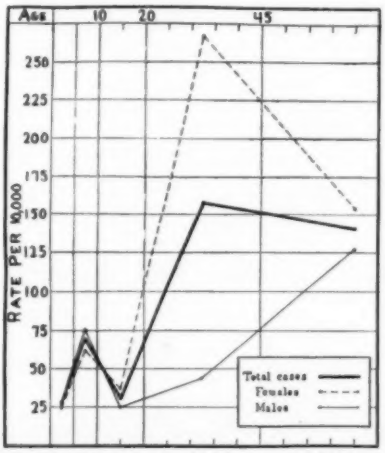

Chart 5.—Comparative pellagra morbidity per 10,000 population, according to age and sex, based on the 740 recorded cases in Spartanburg County up to 1913 and the population of the county as shown by U. S. Census, 1910.

TABLE 5.—Number of Pellagrins in the County in Each Year of Life Up to the Twentieth

Year.....	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Female....	0	0	5	4	9	6	4	3	3	6	6	1	4	3	1	2	4	6	7	7
Male.....	0	1	7	9	5	8	12	8	2	4	5	2	6	1	3	1	3	2	2	2
Total.....	0	1	12	13	14	14	16	11	10	10	11	3	10	4	4	3	7	8	9	9

years we have record of only one case in Spartanburg County, a negro male, recorded as a pellagrin before he was 2 years old. In the third year there were twelve cases, thirteen in the fourth year and fourteen in the fifth year. The number of cases in each of the first twenty years of life for both sexes is shown in Table 5.

4. Siler, J. F., and Garrison, P. E.: Am. Jour. Med. Sc., 1913, cxlvi, 54; First Progress Report, p. 28.

5. This is not the morbidity rate for a single year, but it is the ratio of total recorded cases to the population shown by the U. S. census in 1910. The bulk of the recorded cases of pellagra occurred in 1911, 1912 and 1913.

The figures are not very large, but they are large enough to indicate clearly that pellagra tended to attack children after their second year and that females from 11 to 17 years of age and males 13 years old and over were distinctly less frequently afflicted with the disease. After the seventeenth year pellagra morbidity has been increasingly higher in females, the number of cases rising rapidly until the age of 30, after which age the number of cases for each year gradually diminished, although the morbidity rate per 10,000 population remained high up to the period of old age (see Charts 2, 4 and 5). In males, on the other hand, there was observed no such sharp increase in pellagra, but only a slight and gradual rise in the number of cases, beginning at about

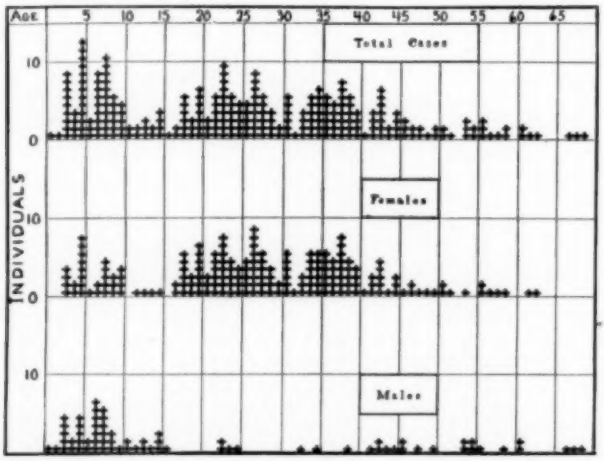

Chart 6.—Distribution of the 253 pellagrins (183 females and 70 males) present in 1913 in the seven villages, I., W., P., Sa., A., Sp. and B., according to age at onset of the disease.

the twenty-third year. The morbidity rate for males reached its maximum in old age, when it was approximately equal to the rate for females of similar age.

Pellagra Morbidity in Seven Closely Studied Mill-Villages.—The intensive house-to-house study of the population of the selected cotton-mill villages, which constituted the chief epidemiological feature of the work of 1913, has furnished an opportunity to study with peculiar accuracy the age and sex distribution of pellagra in a population in which the disease was excessively prevalent. For the present study we have available the approximately complete data in regard to age and sex of all pellagrins and of total population for six villages in Spartanburg County, designated as I., W., P., Sa., A. and Sp., and one mill-

village in Union County, S. C., designated as Village B. The total population of these seven villages was 6,599 and there were present in this population 253 pellagrins, of whom 183 were females and seventy were males. Figure 6 shows the age distribution by years of the total 253 cases, each individual pellagrin being assigned to his age at the time the disease first appeared, and in a similar way the age distribution of the 183 females and of the seventy males. Inaccuracies in the data, similar to those noted above in the data for Spartanburg County, are also evident here.

TABLE 6.—Pellagra Morbidity in the Combined Population of I., W., P., Sa., A., Sp. and B. by Five-Year Age Periods to Age 20 and Subsequently by Decades

Age	Females			Males			Total		
	Population	Pellagrins	Morbidity per 10,000	Population	Pellagrins	Morbidity per 10,000	Population	Pellagrins	Morbidity per 10,000
0- 4.....	447	14	313	514	14	272	961	28	291
5- 9.....	435	15	345	491	19	387	926	34	367
10-14.....	382	4	105	442	9	204	824	13	158
15-19.....	437	18	412	415	1	24	852	19	223
20-29.....	672	52	774	610	4	66	1,282	56	437
30-39.....	418	50	1,196	392	3	77	810	53	654
40-49.....	226	19	841	226	9	398	452	28	619
50-59.....	156	9	577	148	6	405	304	15	493
60-69.....	61	2	328	72	5	694	133	7	526
70-79.....	31	0	0	19	0	0	50	0	0
80-89.....	0	0	0	5	0	0	5	0	0
Total....	3,265	183	560	3,334	70	210	6,599	253	383

By grouping the pellagrins and the total population in five-year periods the distribution shown in Table 6 is obtained. In this table each pellagrin is placed according to his age at the incidence of his disease. The data for total population were obtained by our census in 1913.

The data of this table are presented in graphic form in Chart 7.

The same striking disparity between the morbidity rate of pellagra in females and the rate in males is presented by the figures derived from this intensive study of the mill-village population as has been found in our study of the age and sex distribution of the disease in the total population of the whole county in 1912 and again in 1913.

In children the disease first became important after the age of two, with nine cases in the third year, four in the fourth and thirteen in the fifth. The number of these cases in each year of the first twenty years of life is shown in Table 7.

At about the age of puberty and for a few years afterward, the number of cases was low in both sexes, rising rapidly again after the

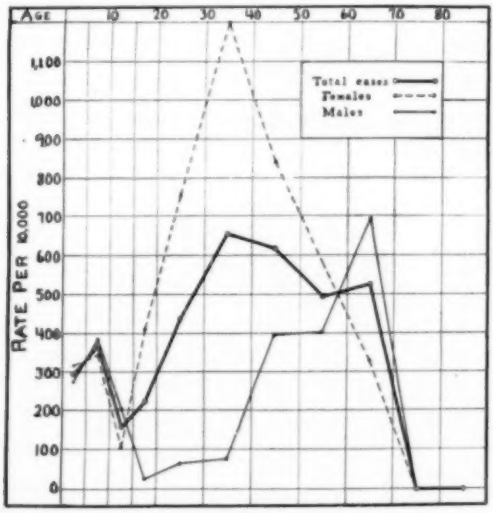

Chart 7.—Pellagra morbidity per 10,000 population of the seven villages, I., W., P., Sa., A., Sp. and B., according to age and sex, based on our census in 1913, data in Table 6.

TABLE 7.—NUMBER OF PELLAGRINS IN SEVEN MILL-VILLAGES IN EACH YEAR OF LIFE UP TO THE TWENTIETH, AGE AT FIRST ERYTHEMA

Year.....	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Female....	0	0	4	2	8	1	2	5	3	4	0	1	1	1	1	0	2	6	3	7
Male.....	1	1	5	2	5	2	7	6	3	1	2	1	2	1	3	1	0	0	0	0
Total.....	1	1	9	4	13	3	9	11	6	5	2	2	3	2	4	1	2	6	3	7

seventeenth year in the females to its highest point in the decade between 30 and 40 years of age, in which period 50 women, or about 12 per cent. of the women in this age period, were pellagrins. In the following decades the morbidity declined rapidly. There were 19 female pellagrins in the fifth decade and only 11 more than 50 years

old. In males, pellagra was somewhat more common than in females in the age period from 5 to 10. After the age of 15 the morbidity rate for males remained very low, comparatively, until the fifth decade, after which the two sexes appeared to be equally subject to the disease. Between the ages of 20 and 50 there were 121 female pellagrins and only 16 male pellagrins, while in the single decade from 30 to 40, there

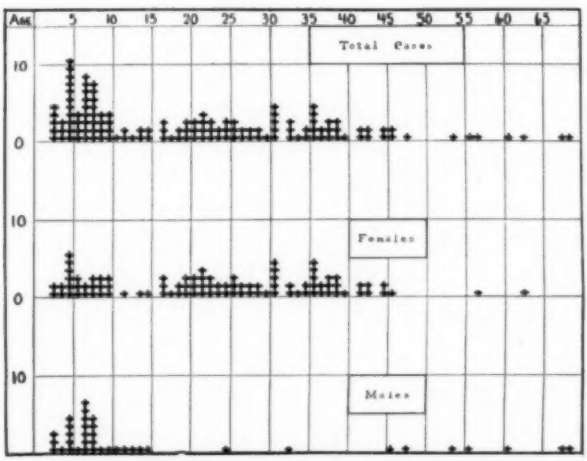

Chart 8.—Distribution of the 131 cases of pellagra (93 females and 38 males) which originated in the seven villages, I., W., P., Sa., A., Sp. and B., in 1912 and 1913, according to age at onset of the disease.

TABLE 8.—Ratio Between Morbidity Rate for Females and Males in Each Age Period in Villages I., W., P., Sa., A., Sp. and B.

Age.....	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69
Females	1.0	0.8	0.4	18.0	13.0	16.7	2.1	1.5	0.4
Males...	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

were 50 female and only 3 male pellagrins. Reduced to its simplest terms, the ratio between the morbidity rate for females and for males in this population was as shown in Table 8.

The marked disparity between the morbidity of males and females during the active period of adult life is clearly evident.

Incidence of New Cases in the Seven Mill-Villages.—The figures just considered related to the total pellagrins present in these seven mill-villages and the total population present there at the time of our

census. It remains to consider the age and sex of the new cases of pellagra which are known to have developed in this population during 1912 and 1913. Some cases which arose in these villages in which the patients moved away before the time of our census in 1913 have been included in the data for this study, and in these instances the non-pellagrin numbers of such families have been added to the total population shown by the census, so that the total population employed in this study was approximately the total population of these villages, free from pellagra at the beginning of 1912. This amounted to 6,594 persons, of whom 3,260 were females and 3,334 males.

TABLE 9.—INCIDENCE OF NEW CASES OF PELLAGRA DURING 1912 AND 1913 IN THE COMBINED POPULATION OF I., W., P., SA., A., SP. AND B., BY FIVE-YEAR AGE PERIODS TO AGE 20 AND SUBSEQUENTLY BY DECADES

Age	Females			Males			Total		
	Population	Pellagrins	Incidence per 10,000	Population	Pellagrins	Incidence per 10,000	Population	Pellagrins	Incidence per 10,000
0- 4....	447	10	224	514	9	175	961	19	198
5- 9....	435	14	322	491	15	305	926	29	313
10-14....	382	3	79	442	5	113	824	8	97
15-19....	422	9	208	415	0	0	847	9	106
20-29....	672	24	357	610	1	16	1,282	25	195
30-39....	418	24	574	392	1	26	810	25	309
40-49....	226	7	310	226	2	88	452	9	199
50-59....	156	1	64	148	2	135	304	3	99
60-69....	61	1	164	72	3	417	133	4	301
70-79....	21	0	0	19	0	0	50	0	0
80-89....	0	0	0	5	0	0	5	0	0
Total...	3,260	93	285	3,334	38	114	6,594	131	199

In this population there developed 131 recognized new cases of pellagra during 1912 and 1913, of which 93 were in females and 38 were in males. The age distribution of these cases is shown in Chart 8. By grouping together the incident cases of pellagra in each five-year perior up to age 20, and subsequently by decades, and comparing these data with the total population in each group the incidence of pellagra for each age period has been ascertained. The figures are presented in Table 9.

The charts (Nos. 9 and 10) show the total population of each age period as a white column and within it a black column, indicating

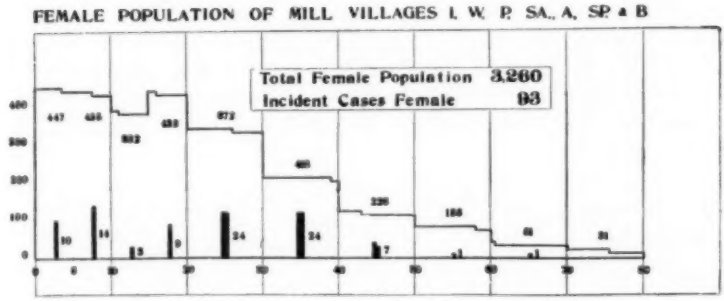

Chart 9.

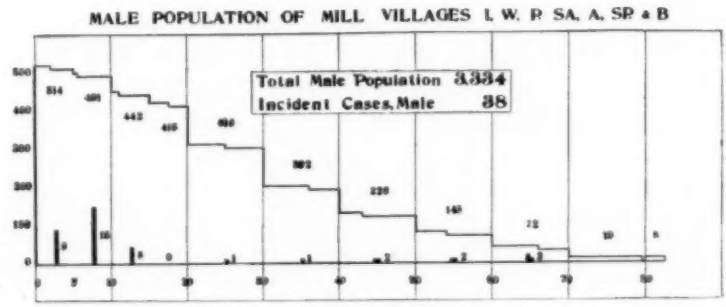

Chart 10.

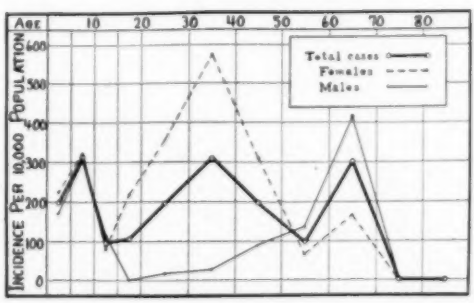

Chart 11.—Incidence of new cases of pellagra during 1912 and 1913, per 10,000 population, in the seven villages, I., W., P., Sa., A., Sp. and B., according to sex and age at onset of the disease, based on pellagra records of 1912 and 1913 and the census of 1913.

exactly by its relative area the proportion of the respective population which acquired pellagra in the two years, 1912 and 1913. These figures show at once the age distribution of the total population as well as of the incident pellagrins and their numerical relationship to each other. The incidence rate in each age group is shown graphically in Chart 11.

The incidence of pellagra in these villages was highest in females between 30 and 40 years of age, nearly 6 per cent. of this age group having contracted the disease during the two years. The next highest incidence was in old men from 60 to 70 years of age, of whom more than 4 per cent. (3 cases in 72 persons) contracted pellagra. The number of individuals in this group is so small that little significance can be ascribed to the incidence shown. In children from 5 to 9 years of age there were 28 incident cases in a population of 926 for this age period, an incidence of slightly more than 3 per cent.

TABLE 10.—Ratio Between Incidence Rate for Females and Males in Each Age Period

Age.....	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	Total
Females..	1.3	1.1	0.7	∞*	22.3	22.1	3.5	0.5	0.4	2.5
Males....	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

* The rate for females in this group was 208 per 10,000; for males it was 0.
∞ = Infinity.

In order to compare more definitely the incidence of pellagra in females with that in males, the ratio for each age group has been reduced to its simplest terms by letting the rate for the males become unity in each instance (Table 10).

TABLE 11.—Ratio Between Incidence Rates for Different Age Periods

Age.....	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50-59	60-69	Total
Females..	0.8	1.1	0.3	0.7	1.3	2.0	1.1	0.2	0.6	1.0
Males....	1.5	2.7	1.0	0.0	0.1	0.2	0.8	1.2	2.7	1.0
Total....	1.0	1.6	0.5	0.5	1.0	1.6	1.0	0.5	1.5	1.0

In a similar manner the ratio of the incidence in each age period to the incidence in the total population of each sex has been reduced to its simplest terms, the incidence for the total females, total males and for the total population being unity in the respective ratios (Table 11).

These figures indicate the relative degree to which each age period was subject to the development of pellagra in the population of these seven mill-villages. Thus in females between 30 and 39 years of age the incidence rate was twice as great as for total females, while between 10 and 14 years the rate was less than one-third of this mean rate.

DISCUSSION

The peculiar distribution of pellagra in respect to age and sex, shown in these statistics, seems now to have been definitely ascertained for the population studied, more accurately, of course, for the seven villages than for the county as a whole. The inequalities of this distribution are pronounced and striking.

Children under 2 years of age were practically free from the disease, and yet from the age of 2 to 10 years children showed an excessive amount of pellagra. Congenital pellagra evidently did not occur in this study. Furthermore, the almost complete absence of pellagra in the first two years of life could hardly be explained as due to a supposed long incubation period of the disease, because there are many known instances in which the typical symptoms have developed in older persons within two months after moving into a pellagrous district, and furthermore, there have been some cases of typical pellagra in children less than a year old observed by various students of the disease. It would seem necessary, therefore, to conclude that children under 2 years of age in Spartanburg County have been physiologically insusceptible to the disease, or else relatively very little subjected or exposed to the causative agencies, or both. After the age of 2 this apparent protection from pellagra was no longer present, and the disease was very prevalent up to the age of 10 or 12 years, when the morbidity rate again declined. Apparently some change occurred at or near the age of puberty, which markedly reduced either susceptibility or exposure to pellagra and which persisted for some years. After the seventeenth year the females were again very subject to the disease, and continued to suffer at an increasing rate to the end of the fourth decade of life, while the males were practically free from the disease during this whole time. From 20 to 29 years of age, women in this population were 22.3 times more frequently afflicted with pellagra than men, and from ages 30 to 39 they were 22.1 times more subject to it. There was certainly some very important sex difference, either of susceptibility or of exposure to pellagra, or both, in these age periods. After 50 the sex difference in relation to pellagra was no longer evident and the old people of both sexes seemed to be about as frequently affected by pellagra as the children. The lower rate in females after 40 may have been due in part to the death of susceptible

individuals in the previous decade of life, but it would seem more probably due to physiological changes in the body associated with cessation of child-bearing and possibly to lessened exposure to pellagra-producing conditions. The rise in the pellagra rate for males at about the same time would seem to correspond with their diminished bread-winning activity and their increased tendency to remain at home.

It is necessary to recognize that the causes underlying this peculiar age and sex distribution have not been ascertained and that speculation in regard to its significance is likely to be erroneous. We are inclined to believe, however, that variation in physiological resistance has been a factor of considerable importance, and more particularly, variation in the vigor of the functions of digestion and nutrition. We also think that variation in degree of exposure to pellagra-producing causes, and more particularly to the supposed infectious agent, may account to some extent for these differences in age and sex distribution.

The high incidence rate of pellagra in children seems to deserve special emphasis because it has not been generally recognized. Many of these cases have been mild and would not ordinarily be brought to the attention of physicians. In the seven mill-villages there were 926 children from 5 to 9 years of age and twenty-nine of these developed pellagra during 1912 or 1913, an incidence rate for the two years of slightly more than 3 per cent. This fact is of particular interest not only because it indicates clearly the high incidence of pellagra in children in those communities where the disease is endemic, but also because of the relation of the incidence rate to the morbidity rate for these children. For the age group of children from 5 to 9 years of age the incidence rate was 313 per 10,000 and the morbidity rate 367 per 10,000, which means, of course, that about 85 per cent. of the cases observed in this age group had existed less than two years. In other words not more than 15 per cent., or about one in seven cases in children from 5 to 9 years of age, had a duration of more than two years. Inasmuch as deaths from pellagra have been rare in these children and the data of the above tables and charts show that few cases persisted into the next five-year age period, it is evident that a large proportion of pellagrin children in these villages must have recovered from the disease in less than three years from its onset. In the adult females between 30 and 39 years of age, on the other hand, the incidence rate in these villages was 574 per 10,000 and the morbidity rate 1,196 per 10,000, showing that there were many chronic cases, although deaths from pellagra in this age group were commonly observed. The general indication is clear that prognosis in pellagra is much better in children than in adult females. We hope to consider in a more definite manner the subject of prognosis in pellagra after our

cases have been followed for another year, but this indication of good prognosis in children is quite evident without any special study and seems worth calling attention to at this time.

Synopsis.—Pellagra was absent or very rare in children under 2 years of age, only very slightly prevalent for the five years following puberty in both sexes and only slightly prevalent in adult males under 50 years of age. On the other hand, it was enormously prevalent and severe in females from 20 to 40 years of age, somewhat less prevalent and nearly always mild in children of both sexes from 2 to 10 years of age, and almost equally prevalent in old people of both sexes. These features of the age and sex distribution are believed to be due in part to differences in physiological resistance to pellagra and in part to differences in frequency and extent of exposure to the disease, especially by proximity to or association with other pellagrins.

OCCUPATIONS OF PELLAGRINS AND THE POSSIBLE ETIOLOGIC RELATION OF OCCUPATION TO PELLAGRA

In the First Progress Report[6] was presented a table showing the occupation of 234 pellagrins on our records. In the present section those cases are again included. We have chosen now to present the cases in three separate groups: first, the pellagrins outside of mill villages; second, the pellagrins in mill-villages not studied by house-to-house canvass, and third, the pellagrins in the six mill-villages most intensively studied. The total number of pellagrins to be considered in these three groups is 726.

The group of pellagrins living outside of mill villages includes 313 individuals (223 females and 90 males). The female pellagrins living outside mill-villages had the following occupations: House work, 171; field work and house work, 35; no occupation, 11; teachers, 3; dressmakers, 2; clerk, 1; total, 223. The male pellagrins living outside mill-villages were distributed according to occupation as follows: Farmers, 37; no occupation, 14; laborers, 12; carpenters, 5; merchants, 5; salesmen, 3; machinists, 3; insurance agent, college student, clerk, butcher, railroad fireman, policeman, painter, blacksmith, printer, motorman and postmaster, 1 each; total 90. The 25 individuals (11 females and 14 males) having no occupation were children, a number of whom were attending school.

In the mill-villages other than those studied by a house-to-house canvass, there were 110 recorded pellagrins (74 females and 36 males). These cases were distributed according to age, sex and occupation as shown in Table 12.

6. Siler, J. F., and Garrison, P. E.: Am. Jour. Med. Sc., 1913, cxlv, 62; First Progress Report, p. 37

The most striking features of these data appear to be the excessive prevalence of pellagra in the adult females engaged exclusively or for part of the time in house-work and the rather high incidence of pellagra in children under the age of 12 years. These observations are similar to those made in 1912 on the relation between occupation and the incidence of pellagra and, taken by themselves, would seem to support the conclusions based on our knowledge at that time, which were summarized in the First Progress Report[7] as follows:

> The excessive prevalence of pellagra in the mill-village population is found largely among women and children at home during the day. Among actual mill-workers the rate of prevalence between the two sexes appears to be about equal.

Additional information on this question has been obtained during 1913. The complete census of several mill-villages has made it possible to compare the pellagrins with non-pellagrins in respect to occupation

TABLE 12.—PELLAGRINS IN MILL-VILLAGES NOT INVESTIGATED BY HOUSE-TO-HOUSE CANVASS, DISTRIBUTED ACCORDING TO AGE AND OCCUPATION

Age	Females						Males					
	No Occupation	House-Work Exclusively	House-Work and Mill-Work	Mill-Work, Full Time	Other Occupation	Total	No Occupation	Farmers	Mill-Work, Part Time	Mill-Work, Full Time	Other Occupation	Total
0-11	8	0	0	0	0	8	13	0	0	0	0	13
12-19	0	12	0	1	0	13	1	0	0	1	0	2
20-29	0	7	11	13	0	31	0	0	0	4	0	4
30-39	0	9	5	3	0	17	0	0	0	7	0	7
40-49	0	2	2	0	0	4	0	0	0	3	0	3
50-59	0	1	0	0	0	1	0	0	0	7	0	7
60-69	0	0	0	0	0	0	0	0	0	0	0	0
Total	8	31	18	17	0	74	14	0	0	22	0	36

and to compare the pellagra morbidity among females at home with the rate among females working in the mills. The data concerning age, sex and occupation of the 303 cases of pellagra (217 females and 86 males) which are known to have occurred in these six villages are summarized in Tables 13 and 14.

The morbidity of the mill-workers and of the remaining population is shown graphically in Chart 12.

7. Siler, J. F., and Garrison, P. E.: Am. Jour. Med. Sc., 1913, cxlvi, 275; First Progress Report, p. 78.

A study of these tables brings out the fact that, so long as we consider only the proportion of house-workers and mill-workers among pellagrous women, the house-workers remain in a considerable majority. It was on data of this sort that our 1912 conclusions were based, inasmuch as exact statistics regarding the relative proportion of women working in the mills and about the house were not available for the non-pellagrin population. Our census study in the six mill-villages has disclosed the fact that the number of male mill operatives is considerably greater than the number of female operatives, instead of being about equal, as we supposed from our general inquiries in 1912, and in the light of this more accurate information the earlier conclusion that female mill-workers were less frequently affected by pellagra than house-workers has become untenable.

TABLE 13.—Total Recorded Pellagrins in Six Mill Villages Investigated by House-to-House Canvass, Distributed According to Age and Occupation

Age	Females						Males					
	No Occupation	House-Work Exclusively	House-Work and Mill-Work	Mill-Work, Full Time	Other Occupation	Total	No Occupation	Farmers	Mill-Work, Part Time	Mill-Work, Full Time	Other Occupation	Total
0-11	37	0	0	0	0	37	38	0	0	0	0	38
12-19	2	2	0	11	0	15	3	0	0	8	0	11
20-29	0	16	21	18	1	56	0	0	0	4	0	4
30-39	0	45	6	12	0	63	0	0	0	5	0	5
40-49	0	22	4	2	0	28	0	1	0	6	1	8
50-59	0	13	0	1	0	14	0	0	0	11	0	11
60-69	0	4	0	0	0	4	3	0	0	5	1	9
Total	39	102	31	44	1	217	44	1	0	39	2	86

In the age period, 12 to 19, in which more than 80 per cent. of the individuals were employed in the mills, the pellagra morbidity was relatively low and the mill-workers were slightly less subject to the disease than those who did not work in the mills. The 94 females who did not work in the mills showed 4 cases of pellagra, a rate of 426 per 10,000, and of the 64 males 3 were pellagrins, a rate of 469 per 10,000, compared with rates of 229 and 150 per 10,000, respectively, in the mill-workers of like age and sex. In the persons over 20 years of age, in both sexes, the pellagra morbidity was generally somewhat higher in the mill-workers than in the total population. The female mill-workers between the ages of 20 and 50 show the highest morbidity.

Synopsis.—Persons engaged in many different occupations were found to be pellagrins, but the greatest number of cases was observed among persons engaged in house-work or remaining at home without

TABLE 14.—Comparative Pellagra Morbidity of Mill Operatives and of the Remaining Population in Villages I., W., P., Sa., A. and Sp., Based on Total Recorded Cases and the Population Statistics of Census of 1913

Age	Mill Workers			Other Persons			Total Population		
	Individuals	Pellagrins	Morbidity per 10,000*	Individuals	Pellagrins	Morbidity per 10,000*	Individuals	Pellagrins	Morbidity per 10,000*
				FEMALES					
0-11	0	0	...	870	37	425	870	37	425
12-19	451	11	229	94	4	426	575	15	261
20-29	245	39	1,592	302	17	563	547	56	1,024
30-39	81	18	2,222	265	45	1,698	346	63	1,821
40-49	26	6	2,308	176	22	1,250	202	28	1,386
50-59	6	1	1,667	116	13	1,121	122	14	1,148
60-69	1	0	0	49	4	816	50	4	800
70-79	0	0	...	26	0	0	26	0	0
80-89	0	0	...	0	0	...	0	0	...
Total	840	75	893	1,898	142	748	2,738	217	790
				MALES					
0-11	0	0	...	960	38	396	960	38	396
12-19	532	8	150	64	3	469	596	11	185
20-29	478	4	84	30	0	0	508	4	80
30-39	296	5	169	36	0	0	332	5	151
40-49	141	6	426	45	2	444	186	8	430
50-59	77	11	1,429	46	0	0	123	11	894
60-69	35	5	1,429	23	4	1,739	58	9	1,552
70-79	6	0	0	11	0	0	17	0	0
80-89	1	0	0	4	0	0	5	0	0
Total	1,566	39	250	1,209	47	390	2,775	86	310

* The figures in the morbidity column of this table indicate the ratio of the number of recorded pellagrins to the number in the respective group of the present population. A considerable number of these pellagrins had died or moved away before the time of our census.

occupation, namely, the adult females and the children under 12 years of age. Occupation in house-work would appear, however, to bear only an accidental relation to this morbidity, because in those villages

concerning which accurate and complete data are available, the morbidity among female mill-workers was practically the same as among the housekeepers. It would appear that our studies have so far failed to discover reliable evidence that occupation has had any definite relation to pellagra morbidity. The excessively high pellagra morbidity in mill-villages would seem to depend on other circumstances affecting the various members of the village community, regardless of whether their days were spent at work in the mill or in other occupations or locations.

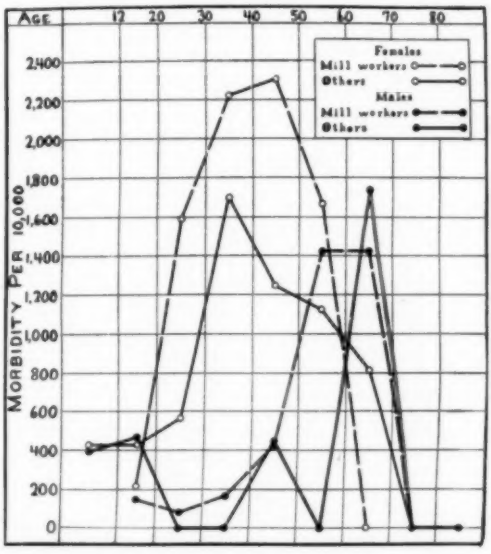

Chart 12.—Comparative pellagra morbidity in the six villages, I., W., P., Sa., A. and Sp., according to age, sex and occupation, based on the total cases of pellagra on record and the population statistics of the census of 1913.

SUMMARY

1. The geographical distribution of pellagra in Spartanburg County, South Carolina, has been uneven, the morbidity being much higher in and near the large centers of population and especially in the cotton-mill villages.

2. Pellagra was found to be about three times more prevalent in the white race than in the negro population of this county. This ratio is not regarded as a true measure of the relative racial resistance to the disease, but rather as the end result of the influence of several factors.

3. Women between 20 and 44 years of age have been most subject to pellagra. Children from 2 to 10 years of age, of both sexes, and

old people of both sexes have also been frequently attacked. Children under 2 years have been rarely affected; adolescents of both sexes and adult males under 50 years of age were relatively free from the disease. Pellagra in children has been relatively benign.

4. The peculiarities of the age and sex distribution are believed to be due in part to differences in physiological resistance to the disease and in part to differences in degree and frequency of exposure to the causative factors, among which proximity to or association with pellagrins seems to be important.

5. No direct relation of occupation to pellagra morbidity was discovered. Indirectly, by determining economic status and environment, occupation was found to have an important bearing on the prevalence of the disease.

MENTAL AND NERVOUS DISORDERS ASSOCIATED WITH PELLAGRA*

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The investigations here published were rendered possible by an invitation to undertake the study of this phase of pellagra extended to the author by the Thompson-McFadden Pellagra Commission. Permission to accept this invitation was readily granted by the Illinois State Board of Administration, to whom my respectful thanks are due. Most valuable assistance was rendered by the physicians of Spartanburg County, by Dr. J. W. Babcock, superintendent, and the medical staff of the South Carolina State Hospital, to one of whom, Dr. E. B. Saunders, I am especially indebted for information and assistance, and finally by the medical officers of the Georgia State Sanitarium. Dr. E. M. Green, clinical director, and Dr. J. W. Mobley, first assistant physician, especially gave of their time and wide experience with ungrudging courtesy. The whole medical staff vied with one another in assisting with the patients and records and contributed materially to such small measure of success as may have been achieved.

The extent of this subject is wide, and the time available was small. Many of the patients were seen but once and there was no possibility of continuous observation over a long period. With these facts in mind, it was thought best to try and observe the conditions at various stages by seeing as large a number of different patients as possible.

The material used comprises that obtained by visits to the homes of known pellagrins in and around Spartanburg, the examination of patients coming, or sent, to the offices of the Pellagra Commission for diagnosis and treatment, a closer study of cases cared for in the Good Samaritan Hospital at Spartanburg, and the investigation of patients and records at the South Carolina and Georgia State hospitals at Columbia and Milledgeville, respectively. To these have been added the results of experience with cases in Illinois.

So widespread is the belief in pellagrous districts, even among physicians, that pellagra is a potent factor in the etiology of insanity, and so greatly is the horror of this disease thereby enhanced in the

* Submitted for publication Sept. 18, 1914.

* From the Illinois State Psychopathic Institute. This paper forms a part of the Second Progress Report of the Thompson-McFadden Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

minds of the people that the question is one of the greatest importance. Yet the actual state of our knowledge concerning the facts is extremely limited. Published statistics vary widely and most text-books, while very vague as to the details, seem to regard insanity as inevitable. Thus Wood says:[1] "It is true that the probable outcome of the ordinary types of pellagra will be insanity, and it is this phase which makes of the disease a great sociological problem."

FREQUENCY OF MENTAL SYMPTOMS

Most of the statistics concerning the frequency of mental disturbance in pellagra are of but small value for various reasons. First, they have been largely collected in hospitals for the insane, and it should be remembered that failure to commit a person to such a hospital is no criterion of the absence of mental disorder. It might also

TABLE 1.—INCIDENCE OF MENTAL SYMPTOMS IN RELATION TO THE NUMBER OF ATTACKS OF PELLAGRA FROM WHICH THE PATIENT HAS SUFFERED

	First Attack	Second Attack	Third Attack	Fourth Attack	Fifth Attack	Sixth Attack	Later Attack	Total No. of Cases
With mental symptoms	12*	17*	9	7	0	2	0	47
Committed as "Insane"	2	2	1	0	0	0	0	5
Without mental symptoms	35	25	10	5	1	0	2	78

* One of these committed suicide.

be said that many persons so strongly believe that pellagra is constantly associated with insanity that commitment may follow the placing of such a diagnosis without further consideration of the actual situation.

Secondly, it is not yet settled whether the recurrent outbreak of the symptoms of pellagra in succeeding years represents new disease each time or merely recrudescence following a period of latency. If the latter is true it would be obviously necessary to wait until the death of an individual before deciding whether he will ever become insane as the result of pellagra.

Thirdly, the statistics are based in the main on superficial estimates of the total incidence of pellagra in any given community, so that the case incidence of mental disorder becomes largely guess-work.

1. Wood, E. J.: A Treatise on Pellagra, D. Appleton & Company, New York, 1912, chap. vi, p. 224.

TABLE 2.—Cases Showing Mental Symptoms in Different Attacks Expressed in Percentages

	No. of Cases	With Mental Symptoms, Per Cent.	Committed as "Insane," Per Cent.	Without Mental Symptoms, Per Cent.
First attack	49	24.5	4.1	71.4
Second attack	44	38.7	4.5	56.8
Third attack	20	45.0	5.0	50.0
Fourth attack	12	58.3	0.0	41.7
Later attacks	5	40.0	0.0	60.0
Total	130	36.2	3.8	60.0

TABLE 3.—Age, Sex and Race Relations to the Incidence of Mental Symptoms

Age	1-10	11-20	21-30	31-40	41-50	51-60	61-70	Over 70
TOTAL CASES CONSIDERED								
	20	11	33	35	10	11	8	2
PATIENTS WITH MENTAL SYMPTOMS								
White males	0	1	2	2	4	3	0	0
White females	0	1	10	13	3	2	2	0
Col. males	0	0	1	1	0	0	0	0
Col. females	0	1	4	1	0	0	1	0
Total	0	3	17	17	7	5	3	0
Proportion of total cases, per cent.	0.0	27.3	51.5	48.6	70.0	45.5	37.5	0.0
PATIENTS WITHOUT MENTAL SYMPTOMS								
White males	9	2	0	1	0	6	2	2
White females	10	6	14	17	3	0	1	0
Col. males	1	0	0	0	0	0	1	0
Col. females	0	0	2	0	0	0	1	0
Total	20	8	16	18	3	6	5	2
Proportion of total cases, per cent.	100.0	72.7	48.5	51.4	30.0	54.5	62.5	100.0

TABLE 4.—Age and Sex Relations Expressed in Percentages

	1-10	11-20	21-40	41-60	Over 61	Total
PERCENTAGE OF PATIENTS WITH MENTAL SYMPTOMS						
Males	0.0	33.3	85.7	53.8	0.0	36.8
Females	0.0	25.0	46.0	62.5	60.0	41.3
Total	0.0	27.3	50.0	57.1	30.0	40.0
PERCENTAGE OF PATIENTS WITHOUT MENTAL SYMPTOMS						
Males	100.0	66.6	14.3	46.2	100.0	63.2
Females	100.0	75.0	54.0	37.5	40.0	58.7
Total	100.0	72.7	50.0	42.9	70.0	60.0

The last source of error is a very important one. The experience of the Thompson-McFadden Pellagra Commission has demonstrated that, when an intensive study of a given pellagrous district is undertaken, far more cases are discovered than would be estimated from the most careful questioning of the physicians of that district.

In order to arrive at some data on this question the case records of 130 pellagrins, collected without any kind of selection except a positive diagnosis, have been analyzed and the results are presented in Tables 1 to 4. In preparing these tables no attempt has been made to subdivide the mental picture into different types, a point which will be considered later. It may be stated, however, that the great majority of cases included as "with mental symptoms," but not committed as "insane," were examples of a type which will be described as symptomatic depression. Such mental disturbances as well as milder forms of delirium occur in connection with many different diseases, especially the acute and chronic infections, and it may be objected that they do not constitute "insanity." In reply to this it is only necessary to point out that this latter term is not a medical one at all, and that no distinction can scientifically be made.

In this series of one hundred and thirty unselected cases, mental symptoms were present in fifty-two (40 per cent.), and of these, five (3.8 per cent.) were adjudged insane, while two others committed suicide. Certain other features also deserve mention. It will be noted that mental symptoms appear to be progressively more frequent the greater the number of the attacks. (This does not hold true in the above tables for cases having more than four attacks, but this may possibly be due to the small number of such examples.) In Tables 3 and 4, it is well shown that children with pellagra do not as a rule show

any mental disorder, and one may add from personal observation that they are generally not very ill with the disease. From the figures given it would appear that males between the ages of 20 and 40 suffer with mental symptoms far more than do females.

This is probably not without significance, although it must be admitted that the number of cases is very small (seven). When it is remembered that men of this age but rarely contract pellagra, it suggests that those who do are in all probability below the average in general make-up and hence especially liable to suffer from mental disorder.

The greatest case incidence of mental disorder in females, on the other hand, occurs between the ages of 41 and 60; that is to say, during the climacterium, a period during which, as is well known, women are especially prone to mental disturbance.

To supplement these figures, a similar analysis of a series of thirty-four consecutive cases studied by me and forming part of the material on which the later description of types is based, showed results entirely in keeping, except that the numbers are too small for subdivision into age groups. The percentage showing mental symptoms was 38.2. There were ten children of 10 years or under, none of whom showed any mental disturbance. The average age of those with mental symptoms was 41.5 years and of those without mental symptoms, 18.5 years.

As might be expected, there is also a correlation between the appearance of mental symptoms and the severity of the pellagra attack, as illustrated by the mortality given in Table 5.

TABLE 5.—Case Mortality in Relation to Mental Symptoms

	No. of Cases	Deaths	Percentage Mortality
With mental symptoms	52	10	19.2
Without mental symptoms	78	2	2.6
Total	130	12	9.2

As a further illustration of this same point, it was found that in a series of eighteen patients, cared for and examined in the hospital provided for the Commission, who were admitted mainly because of the severity of the pellagra attack and the need for special attention, sixteen with an average age of 44 (23 to 95), showed mental symptoms, the exceptions being aged 10 and 15 years, respectively.

With the object of studying the question as to whether pellagra gives rise to a chronic "insanity" a list of all cases committed to the Columbia State Hospital from Spartanburg County from Jan. 1, 1912, to July 1, 1913, was secured, and these cases were investigated to determine how many were suffering from pellagra. These investigations were made possible by the courtesy of Dr. J. W. Babcock, super-

intendent, and the medical staff of the South Carolina State Hospital, the excellent records in the office of the Pellagra Commission and the physicians of Spartanburg County.

In 1912 sixty-five persons were adjudged insane in Spartanburg County, of whom eleven were stated to be pellagrous at the time of commitment. This diagnosis was confirmed at the State Hospital in all but one who had recovered from his attack at the time of admission. Besides these, nine others are reported as having pellagra at the time of admission to the hospital. In the first six months of 1913, twenty-four persons were adjudged insane, although only twenty-two were admitted to the State Hospital. Four were stated to be pellagrous on the commitment papers and to these must be added three found to have this disease when received at the hospital.

The population of Spartanburg County at this period was stated to be 83,465. The proportion of pellagrous persons living in the county, according to the figures of the Thompson-McFadden Commission in 1912, was 44, and in the first six months of 1913, 55 per 10,000.

These facts may be expressed in the accompanying table (Table 6).

TABLE 6.—CERTIFIABLE INSANITY IN PELLAGROUS AND NON-PELLAGROUS PERSONS IN SPARTANBURG COUNTY *

	Total Number of Persons Committed	Number of Pellagrins Committed	Certified Insane per 10,000 Population	Certified Insane per 10,000 Pellagrins
1st. 6 mos., 1912...	28	9	3.3	245.2
2d. 6 mos., 1912...	35	14	4.2	381.5
1st. 6 mos., 1913...	24	7	2.9	152.2

* It should be noted that the population has been considered as remaining constant throughout, and also that the number of living pellagrins in the first and second halves of 1912 has been regarded as equal. While not accurate, this will suffice for the present purpose. The figures for the whole of 1912 would be correctly given as the sum of those for the two halves of that year.

These figures as to the case incidence of insanity are somewhat smaller than those given by Grimm,[2] who found 7.5 per cent. insane of 1,436 cases. Presumably this refers to those who were certified as insane, and it is probable that the percentage is somewhat high for the reason that many of the milder cases of pellagra would not come under observation unless they were sought. Especially is this true, in the experience of the Thompson-McFadden Commission, for pellagrous

2. Pub. Health Rep., U. S. Pub. Health Service, March 7, 1913.

children in whom, as the figures already given amply demonstrate, mental symptoms are exceptional.

One other feature of the relation between insanity and pellagra, which has already been briefly mentioned, requires further consideration. That is the extraordinary frequency of pellagra arising in hospitals for the care of the insane. This fact of almost universal experience is well illustrated by the situation at Milledgeville, Ga. In Tables 7 and 8 are given, respectively, the numbers of cases of pellagra arising within and without the walls of the hospital in which there was an association with certifiable insanity.

TABLE 7.—PATIENTS ADMITTED WITH PELLAGRA ALREADY DEVELOPED *

	White						Colored						Total		
	Male			Female			Male			Female					
	Admissions	Pellagrous	Per Cent.	Admissions	Pellagrous	Per Cent.	Admissions	Pellagrous	Per Cent.	Admissions	Pellagrous	Per Cent.	Admissions	Pellagrous	Per Cent.
1910	338	..	...	264	..	...	207	..	...	187	..	...	996	56	5.6
1911	365	14	3.8	281	31	11.1	212	5	2.4	206	20	9.7	1,064	70	6.5
1912	375	21	5.6	311	18	5.8	226	11	4.9	196	33	16.8	1,108	83	7.4
Total ...	1,078	35	3.2	856	49	5.7	645	16	2.5	589	53	9.0	3,168	209	6.6

TABLE 8.—CASES PROBABLY ARISING WITHIN THE HOSPITAL *

	Average Daily Population	White		Colored		Total No. of Cases	Per-centage
		Male	Female	Male	Female		
1910	3,276	..	..	..	..	114	3.5
1011	3,383	12	16	10	61	99	2.9
1912	3,424	35	27	21	97	180	5.3

* These figures are taken from the annual reports of the Georgia State Sanitarium.

The population of the state of Georgia, according to the 1910 census was 2,609,121. If we accept the proportion of certifiable insanity for Spartanburg County as approximately correct for the state of Georgia, this would mean that in 1910 there were approximately 900 pellagrins (this figure is probably far too small, H. D. S.), or 3.4 per 10,000 of the population. On the other hand, the average daily

population of the hospital was 3,276 with 114 cases of pellagra, or 348 per 10,000, practically one hundred times as many as in the population outside. Experience in Illinois would tend to bear this out.

No satisfactory explanation of these facts has yet been offered. There are, however, several possibilities. First, if, as I fully believe, pellagra is an infectious disease, these hospitals may be endemic foci in which the opportunities for transmission are especially favorable. Secondly, it may be that the conditions of life are such as to cause pellagra, either by deficiencies in dietary, or positive intoxication by spoiled food or other means. Thirdly, and this is a possibility which has been too little considered, the conditions of life in such a hospital or the constitution of the persons therein confined may be such as especially to favor the onset of pellagra whether the actual cause be a living virus, a dietary deficiency or an intoxication. In discussing these possibilities it must be conceded that the only explanation for a special focus of infection in such a hospital would be the collection together of a large number of infected individuals sent to the hospital because of the occurrence of "insanity." This would not explain the sequence of events at the Peoria State Hospital and other institutions of like character in Illinois where the outbreaks appeared to start in these widely separated localities, while the number of cases in the state generally was certainly small. Some explanation is also needed for the rarity with which doctors or attendants in these institutions become affected. I know of no instance in Illinois. In Georgia but one was reported (J. E. H., white, male, attendant, on June 19, 1913) in the years 1910 to July, 1913.

The relation to dietary has already been discussed in the Report of the Illinois Pellagra Commission, 1913, so that there is no need to enter on that question here.

From the above consideration it therefore seems justifiable at present to state that evidence points to the conclusion that there is something in the make-up of those persons who suffer from faulty nervous organization, and especially of those who show character traits leading to what is called "insanity," which renders them more prone to affection with pellagra. This would be entirely in keeping with the statistics concerning the frequency of association between pellagra and insanity given above and elsewhere. It is too often forgotten that statistics merely establish correlations and do not indicate causal relationships. The importance of this view on the relation between pellagra and insanity will become more obvious from a consideration of the types of mental disorder which will be next considered.

TYPES OF MENTAL PICTURE

The literature dealing with the forms of mental picture occurring in association with pellagra is not extensive and has been reviewed in an excellent article by Gregor[4] who also gives the results of his own investigations on this subject. He emphasizes the importance of distinguishing between the mental disorders which may be directly attributed to pellagra; i. e., are due to cerebral changes brought about by the pellagra toxin, and those which have only a secondary relation to it. As will be seen from the report which follows, my results agree in the main with those of Gregor, and there is but little need to discuss his findings separately.

The type of mental picture has also been studied in some detail at the Georgia State Sanitarium, where there is a large mass of material available for the purpose. At this hospital a system of classification has been adopted, under the advice of Dr. Adolf Meyer, which is free from objection, but which makes no attempt to particularize as to the relation between the pellagra attack and the psychosis. Such a method is unquestionably wise where the data are as yet scanty and the material undigested. Under this system all cases in which pellagra seems to have some relation to the onset of the psychosis are grouped together under the general title of "Psychoses Accompanying Pellagra." This group is then subdivided according to the condition-picture presented into subheads corresponding with the Kraepelin classification in general use. Thus there appear: Infective-exhaustive, manic-depressive, dementia praecox, involutional melancholia, general paralytic, paranoic and senile types.

At present, however, it seems justifiable to speak a little more definitely concerning the meaning of these types and their relation to pellagra. The situation, indeed, is much the same as that concerning the relation of many other general diseases to mental disturbance. As is well known, similar varieties of picture are met with in typhoid fever, yet they are not grouped separately because of this association. We recognize, it is true, that the toxins of this disease, like many others, directly injure brain, as well as other body cells; and that, in consequence of this damage, certain disorders in function, such as delirium, appear, which may be regarded as the direct result of the infection. On the other hand, there may appear a dementia praecox picture or a manic-depressive reaction and these cases run a similar course to that of other examples of these types in which there has been no such infection. It may be said that there are but few to-day who regard typhoid fever as more than a precipitating cause. Personally, I regard such

4. Jahrb. f. Psychiat. u. Neurol., 1907, xxviii, 215. Trans. by A. Alleman in Alienist and Neurologist, 1911, xxxii, No. 4.

reactions as this, whether following a specific fever or other somatic disease, or whether appearing in connection with some psychological difficulty, as the way of meeting difficulties of all kinds which are peculiar to this particular individual as the result of inheritance and experience.

Viewed in this light a dementia praecox type of picture and course is not a particular kind of disease, but merely the natural outcome of the particular kind of make-up with which the individual is endowed when placed face to face with difficulties which call for special adjustment. Thus, pellagra would not be the cause of the dementia praecox syndrome, but merely the last straw which brings the individual's modes of adjustment into prominence and demonstrates the odd and inadequate manner of doing things which have always been present, but which have not been specially obvious hitherto.

Indeed, there is another view of the relation between pellagra and insanity which deserves serious consideration and which has hitherto been but little discussed.

It is quite within the bounds of possibility that the actual relation between the functional psychoses (including dementia praecox) and pellagra is somewhat the reverse of that more usually accepted. That the defective construction, whatever it be, which is responsible for the poor adaptability and peculiarity of make-up indicated by the particular stamp of these disorders, predisposes to the development of pellagra. It is certainly a fact that the disease is extremely frequent among the chronic insane, most of whom represent late stages of the dementia praecox personality. This possibility should not be forgotten when considering the epidemiology of pellagra.

The relation of pellagra to psychoses due to more definite brain disease or degeneration, such as the presenile, senile and arteriosclerotic dementias, is a somewhat different question. That pellagra occurs in combination with them is unquestionably true, and it may be that such involutional changes and diseases as involve not only the brain but also the organs of the whole body, predispose to affection with pellagra. It is also conceivable that an intoxicative disease such as pellagra might favor the early onset of involutional change, or even actually provoke arterial degeneration in the course of time. But the relation of pellagra to the dementia thus arising would even then be secondary rather than direct.

The so-called general paralytic type has given rise to much discussion and deserves some special consideration, although I have so far been unable to see cases in which this description seemed justified. That pellagra occurs in individuals suffering from dementia paralytica is a fact of observation, as in a case recently seen with Dr. O. S.

Ormsby in Chicago. But this is not what is implied by this description. The cases here grouped have all been rapidly fatal and the picture presented is that of the final stage of dementia paralytica. It is not claimed that they run the whole course of that disease. To quote from the report by Green of Milledgeville, Ga., the features which lead to such a grouping are: "Exaggeration or loss of knee-jerk, speech disturbance [possibly a dysarthria due to stomatitis, H. D. S.], tremors, muscular incoördination, pupillary inequality or irregularity, convulsions and sensory disturbance." The case records of examples which I was able to study at the Milledgeville hospital speak of extreme disorientation with confusion and a muttering incoherence, so that but little information can be obtained from the patient who leads a more or less vegetative existence, does nothing for himself and voids urine and feces in the bed. The picture thus described suggests an extreme degree of general intoxication with central and possibly at times peripheral neuritis. It resembles in many respects the severe toxic forms of infective fevers, such as typhoid, and there seems but little justification for regarding it as especially comparable to dementia paralytica. It is not the extreme nervous disorganization which is characteristic of general paralysis, and it is unfortunate that a name with a specific significance should be used to describe a condition which may result from many different causes.

For purposes of description the types of mental disorder associated with pellagra may be grouped as follows:

Group I. Disorders directly due to the pellagra toxin (or toxins).

1. Symptomatic depressions.
2. Delirious pictures.

Group II. Disorders based on peculiarities in personal make-up, the "attack of insanity" being precipitated by pellagra.

1. Manic-depressive disorders.
2. Hysteria.
3. Psychasthenia.
4. Dementia praecox.
5. Paranoic developments.

Group III. Disorders due to definite brain changes with pellagra merely as a complication.

1. Arteriosclerotic dementia.
2. Senile dementia.
3. Presenile psychoses.
4. General paralysis of the insane.

The disorders in Group I may be considered in some detail, whereas the others will be passed over more briefly.

I. *Symptomatic Depressions.*—This type of disturbance is by far the most frequent, if one includes the cases outside a hospital for the insane. They are but seldom committed. They have been described by Gregor under the title of neurasthenic type, but the name here used seems preferable for the reason that while neurasthenic features are present, yet there is a decided attitude of depression, sometimes without any very definite objective signs of fatigue. The main characteristic of them is that the attitude of depression runs parallel with the other manifestations of pellagra, improving as they improve and becoming worse as these other symptoms become more severe.

The picture presented is that of a more or less hopeless sadness with all that this implies in regard to the activities of the body as a whole. There is a general lowering of tone, energy and attention are more or less difficult, thinking is difficult and activities are diminished. Obviously the exact mode of expression will vary with the personality of the patient, just as the words he uses to express his feelings depend on his personal experiences and habits of adjustment. As illustrations of the type most commonly met, the following quotations from cases observed in Spartanburg may be given: In expressing the color of the mood, "so blue I couldn't stand it hardly . . . seemed like I couldn't stand it if I couldn't sit down and cry"; "afraid I'll not get better"; "depressed and down-hearted"; "can't get cheerful"; "can't ever look forward to being any better." At times this is amplified by similes such as: "feel like I was lost . . . my soul was going to be lost and going to torment . . . didn't feel like I could get forgiveness for my sins." The lack of energy and feeling of inefficiency are shown in "energy and ambition all gone"; "can't do nothing, can't work or hold out"; "lost interest . . . it's hard to work"; "so tired all the time, no ambition"; "I just feel helpless"; "I used to be one of the best housekeepers and now look at my house." The difficulty in thought is shown in: "can't get my mind on anything"; "it's difficult to think"; "my recollection is mighty short"; "I'll get up from the porch to do something and forget what it is before I get into the house."

Sometimes there is more or less well-marked apprehension without any definite fear, e. g., "I feel as if something is going to turn up"; "so nervous I scream when anything happens." etc. At times this becomes definitely an anxiety expressed not only in words, but also by restless agitation. This has seemed to be true especially in persons during the involutional period of life and hence probably connected with the somatic changes which are then in progress, but it does also occur in younger individuals. Well-marked examples of this kind would naturally be included with the presenile psychoses or involu-

tional melancholia. In such case the pellagra is not the direct cause, but rather an exciting or perhaps purely complicating disease. Thus, for instance, I recently had under care in Illinois a woman in comfortable circumstances in life, who at the age of 58 developed an anxious agitated depression for which she was sent to a sanatorium. In the course of a few months she improved, although still depressed, and was returned to her home where she developed pellagra and became more worried and depressed, with finally the necessity of commitment at least three months after the onset of pellagra, but with active manifestations in the skin and gastro-intestinal tract. The condition ended fatally in a few weeks. Here unquestionably the sequence of events suggests that pellagra was merely a complicating disease and that the general bodily state expressed in the psychosis was a predisposing factor to, rather than the result of, its development. No other cases of pellagra had been known in the town in which this patient lived, although I am informed, one had occurred a year earlier in the sanatorium to which she was first sent.

Delirious Pictures.—By the term delirium is implied a state characterized clinically by clouding of consciousness together with sense-falsifications, especially of illusory character, the reactions of the patient in word and act being conditioned by this dream-like state. The vast majority of such condition-pictures are the result of intoxication of the brain with consequent general lowering of functional activity which involves first and most the highest cerebral levels. All degrees are met with in pellagra as in other intoxications. In the milder forms the periods of clouding may be quite brief and episodic. In such cases, in the intervals when consciousness is practically clear, the general attitude is one of symptomatic depression similar to those described above. Indeed, it is not uncommon to find that the more severe forms of depression give a history of occasional and transient sense-falsification with apprehensive content and more or less fear-reaction. Such, for instance, is true for Case 1, recorded below, while Case 2 represents a more severe and permanent clouding with practically complete amnesia for the period on recovery.

CASE 1.—*Symptomatic depression with episodic clouding, sense-falsification and apprehension. Central neuritic syndrome and fatal outcome.*

B. S., white woman, aged 35, observed first at home and later in the Good Samaritan hospital. The family history as far as obtained was negative for mental and nervous disease. The patient was stated to have been healthy except for malaria in childhood. The first attack of pellagra appeared in April, 1910, and subsided in the following month, but was accompanied by some depression. The second attack was very similar and appeared in April, 1911.

The third attack of pellagra was more severe and began in April, 1912. This was accompanied by severe gastro-intestinal symptoms and was still present in July when she was examined by the commission, who state that she then was very weak, much depressed and did not seem at all times to be quite clear in

her mind. This outbreak gradually subsided, but the erythema recurred again in December, 1912, with an exacerbation in January or February, 1913.

Mental picture: July 16, 1913. The patient appeared very dull and apathetic, intensely depressed, "life is not worth living," spoke in a low, rather monotonous voice, slowly and only with frequent urging. She seemed to be entiely clear and perfectly oriented as to her surroundings and the situation. When left to herself she lay in bed almost without movement, paying but little attention to what was taking place around her.

In answer to questions she expressed a feeling of fear, at times severe, as if "something going to get me." She mentioned the occurrence of "bad dreams" in which she would see horrible things, animal forms which she could not describe. She would also hear voices, even when awake, some of which were recognized, others were strange. They frightened her but she could not give the content more than to say that they were "just calling me." There was at the time of examination a full realization that they were imaginary but "they just come by spells" and at such times seemed real. In answer to a leading question she stated that at such times she did not feel clear in her mind.

Such periods as this came irregularly and lasted perhaps a day but she could not give any details as to frequency. The picture of hopeless apathy continued during the week that she was under observation, without the appearance of any objective evidences of clouding or apprehension. There was, however, a rapid development of signs of a "central neuritis" reaction, gross exaggeration of deep reflexes, bilateral extensor plantar reflex, slight jactatoid movements, nausea and vomiting. In spite of a temporary improvement in the last few days of July, the patient died August 9, 1913.

CASE 2.—*Delirious type. Severe clouding of consciousness with sense-falsifications of dream-like character and of depressive and more or less horrible content. After about four weeks a brief period of apathetic stupor and recovery with amnesia; subsequent exacerbation with fatal outcome.*

S. M. P., white woman, aged 23, housewife. Admitted July 11, 1913. The friends and relatives were very ignorant and the history is consequently not full. As far as could be determined, the family history showed nothing of importance for two generations. The patient was always healthy and had no serious illness. She had some attacks of "fever," but was at no time out of her head. The family were in poor circumstances and she had no schooling. She was described as of quiet, retiring disposition, high-tempered and "some selfish." She was, however, contented and cheerful, "would sing right smart" and worked steadily. Always scrupulously neat and clean, "an excellent housekeeper," "nothing ever out of order." She was married about two years ago; has been happy and has one child about 1 year old.

Pellagra: The first attack occurred in the summer of 1912, five months before the birth of her child. She then had a characteristic erythema of the hands with stomatitis and diarrhea. She was not very ill and is said to have had no mental disorder except "some loss of memory" and a general malaise. These symptoms all cleared up during the summer, although there is said to have been some scaling of the hands more or less until the present attack. Towards the end of May, 1913, the hands again became sore and soon after there appeared sore mouth and diarrhea.

Mental disturbance: About the beginning of the last week of June, 1913, the patient became "queer in her head." She seemed "to be hearing voices and talking to them." At first more or less intermittent this condition has become worse and practically continuous with increasing restlessness and fearful excitement. Many of her utterances were quite unintelligible even to her relatives, but the general trend is illustrated by such remarks as she had "seen her mother dead," her "head cut off," etc. At times she would suddenly "jump up like she was going to run away," and the restlessness had become so extreme as to make it difficult to care for her. During this period she had been growing steadily weaker and had emaciated badly.

When admitted to the hospital she was extremely ill, with severe and characteristic erythema, stomatitis and diarrhea. When seen by me, July 14, 1913, no very complete examination was possible owing to the extreme illness of the patient, but no evidence of other somatic disease was discovered. Neurologically there was marked exaggeration of the deep reflexes but without clonus, and the plantar reflexes were of flexor type. Constant restless movements were present, tossing about in bed, pulling at the bed clothes and even trying to get out of bed. All these movements were feeble and tremulous but showed no incoordination and there were no convulsive jerkings or twitchings.

All the time the patient was muttering, with occasional crying or apprehensive screaming. Much of what she said could not be understood, partly because of the low muttering, and partly because of the dysarthria due to severe ulcerative stomatitis. Samples of spontaneous utterances are: "Give it here . . . give it here . . . Oh! get up . . . get loose from there . . . I can't do nothing . . . (pulling at the bedclothes and looking around apprehensively) . . . I wouldn't use you that way . . . Oh! . . . Oh! . . . you're on my dress . . . I want my dress . . . (cries and moans fretfully and becomes unintelligible)." "I go up and go all over the place . . . go from here to the mill . . . and never know what is the matter . . ." "Annie . . . Annie . . . Annie . . . Oh! . . . Oh! dear (screams) . . ."

During this time she was apparently taking no notice of her surroundings, paid no attention to the examiner or her sister when they entered the room nor to the fact that someone was sitting close beside her. By speaking loudly and persistently it was possible to gain some degree of attention and even some degree of relevancy in response. When asked her name she did not give it but when asked to spell it said somewhat slowly and monotonously, "R - i - n - e - e - n - h - e - a - e - a - h - e - a - t - a - t - a - t" (her maiden name was Rhinehart). She gave the name of her home town correctly, but when asked her father's name gave that of her husband. When asked if she was sick she replied, "Of course I am . . . Go away from here . . . I don't want to talk to you . . . I want to go home . . . Annie . . . Annie . . . Oh! . . . Oh! . . . dear." Questioned as to her baby she said that "she (the baby) is dead." This is not true but is an illustration of the depressive content of the ideas. No answer indicating any grasp of where she was could be obtained and she apparently failed altogether to recognize her sister or brother-in-law.

She virtually did not sleep the following night, but screamed and yelled as if in fear or in pain. The next morning, however, she was a little brighter when roused, recognized her sister and called her by name, but immediately again became more clouded and presented a picture much as before.

July 17 she was obviously clearer and more easily roused but fretted and moaned much of the time. She then stated that she "felt terribly bad" and spoke spontaneously of a visit from her sister and mother (the latter had not been there) and added that she had not seen her husband. With regard to herself she said "seems like I have just given way and haven't got any use to myself . . . I can't get up . . . couldn't do nothing." When questioned about her baby she replied that she was "doing nicely, thank you." She very speedily became tired and more fretful and denied any knowledge as to her whereabouts.

From that time she became gradually brighter when roused but at the same time more heavy and apathetic when left to herself. It was not until July 22 that she was able to recall the name of the hospital or the examiner, although these had been told to her repeatedly. At this time she said she was "feeling good" but very tired. She stated "I've got my mind now . . . have for a long time . . . I used to didn't have none, didn't know nothing." In answer to question she professed to be entirely ignorant as to what had happened for two or three weeks but came to herself "last week." She spoke of the period

as being "all like a dream," but was apparently unable to remember any of the dream.

Coincident with the improvement in the mental state the pellagrous symptoms had been improving. The skin eruption was almost gone on July 20 and the diarrhea, after becoming gradually less, ceased altogether about July 22. She remained weak but clear mentally until September 1, when she became stuporous and died September 7.

Occasionally, periods of delirium recur several times in relation with exacerbations in the general manifestations of pellagra. One such example was seen at Milledgeville in the case of T. S., a colored man, who had four such brief periods of apprehensive excitement in which he vaguely remembered horrible "dreams" of being pursued by wild animals and tortured by persons in his environment with whom he fought. These "dreams" explain his conduct as observed during the attacks and each occurred in association with an exacerbation of diarrhea.

The relation of pellagra as the cause of such attacks is fully intelligible, but it should be remembered that different individuals show different relations to intoxication. Some very easily become delirious from alcohol or mild infectious fever; others seem able to resist much larger doses and more severe infections. It is thus generally recognized that the persons who readily develop delirium are poorly constructed in some way. The fact that delirium occurs so frequently in pellagra is capable of two explanations. Either the toxin is extremely virulent, or the individuals who suffer from pellagra are especially those of poor nervous organization. This latter possibility is in keeping with the suggestions already made in this direction.

II. *Disorders in which the Character of the Picture is due to the Personality of the Individual Affected.*—It would be entirely out of place here to attempt to describe these pictures. They differ in no way from other examples of such types not associated with pellagra. It is true that the pellagrous intoxication may give rise to a delirious stamp which may render the recognition of the type more difficult, but such features, as in the deliriums already described, will run a course parallel to the other pellagrous manifestations, whereas the elements in the disorder belonging to the personality of the patient will remain more or less independent of them.[5] This is also the case with examples of such psychoses arising in connection with specific fevers. Dementia praecox precipitated by a puerperal infection may be recognizable at first only as a delirium, which disappears with the subsidence of the infection, while the peculiar traits of conduct which make up the dementia praecox picture become thereby more and more obvious.

It may be said, then, that disorders of this kind run a similar course with a similar outcome (except that the pellagra brings with it a far

5. See Case 2 "Pellagra in Illinois," THE ARCHIVES INT. MED., 1912, x, 162.

greater menace to life) to that of cases arising with some other factor as a precipitating agent. The dementia praecox types result in what is called deterioration or dementia, the manic-depressive modes of reaction subside after a shorter or longer time without dementia, and so on.

In cases of this kind which have been investigated by me, evidences of the type of personality which results in such developments have been demonstrable before the onset of pellagra. An excellent illustration is afforded by a typical outbreak of manic excitement coincident with the appearance of pellagra which led to the first commitment of the patient.[6] The anamnesis revealed evidence of a manic-depressive type of make-up for several years before.

An excellent example of a dementia praecox picture, with apparent recovery, was seen at Milledgeville. A very full katamnesis was obtained in which it was learned that the fancies and imaginations with peculiar forced reactions had been present, although unknown to relatives, for at least nine months before the outbreak of pellagra, which did not become quite definite until after admission, although suspected at the time when she was received. Another patient was seen at Columbia with considerable deterioration, of the dementia praecox type, who had been admitted to the hospital on several occasions with attacks of pellagra, but in whom the mental disorder, as stated by Dr. Saunders, had been present at least one year and a half before the first attack of pellagra.

Below is published in detail another case (Case 3), probably belonging to the dementia praecox group, but with certain other features of nervous disease which seemed worthy of record. The absence of any parallelism between the pellagra and other nervous manifestations is here obvious.

These illustrations might be multiplied without advantage, sufficient having been said to illustrate the point under consideration. It may be that cases occur in which the sequence here claimed cannot be demonstrated, but where it has been possible to obtain sufficient information, no case has yet been presented to controvert this claim. Both at Milledgeville and Columbia an effort was made to see every pellagrous patient who had been detained as an example of chronic insanity.

With regard to Group III, there will be but little objection to the views expressed, that the pellagra and nervous disease are separate disorders, although it is possible that some degree of correlation may exist, in that one may predispose to the other. The question of a general paralytic type has already been discussed and need not detain us here.

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6. See Case 3, "Pellagra in Illinois," THE ARCHIVES INT. MED., 1912, x, 166.

FREQUENCY OF THE DIFFERENT TYPES OF MENTAL PICTURE

This subject may be considered under two headings. First, the frequency in a series of cases of pellagra, and second, the frequency in a series of cases committed to a hospital as "insane." The material at hand is not entirely satisfactory for this purpose owing to the short time available. For the first part of the question, use will be made of the cases in which the patients were seen and examined by me, and of the 130 observed by the Pellagra Commission. The information in these latter cases is not always sufficient to justify a positive conclusion, but the errors will be small.

TABLE 9.—TYPES OF MENTAL DISORDER IN A SERIES OF PELLAGRINS

	Thirty-four Unselected Cases Seen by the Author		One Hundred and Thirty Unselected Cases Seen by Commission		Total Unselected Cases		Eighteen Hospital CasesSelected for Severity	
	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.	No. of Cases	Per cent.
Group I—								
Symptomatic depression	9	26.5	41	31.5	50	30.5	10	55.5
Delirious pictures.....	2	5.9	10	7.7	12	7.3	2	11.1
Group II—								
Manic-depressive disorders	0	0.0	0	0.0	0	0.0	1	5.5
Hysterical disorders.....	1	3.0	0	0.0	1	0.6	0	0.0
Dementia praecox disorders	0	0.0	1	0.8	1	0.6	1(?)	5.5
Group III—								
Arteriosclerotic dementia	0	0.0	0	0.0	0	0.0	1	5.5
Presenile phychoses.....	1	3.0	0	0.0	1	0.6	0	0.0
Senile dementia.....	0	0.0	0	0.0	0	0.0	1	5.5
Total	13	38.2	52	40.0	65	39.6	16	88.8

For the second part, use has been made of the thirty pellagrins committed to the Columbia State Hospital from Spartanburg County. To these are added the figures obtained from the annual reports of the Georgia State Sanitarium. Many of the records of these cases and some of the patients were investigated by me, so that some discussion is permissible.

From Table 9 it will be seen that in a series of 164 unselected cases of pellagra, mental symptoms directly attributable to this disease occurred in 62 or 37.8 per cent.; that 2 (1.1 per cent.) presented a psychosis depending on peculiarities in personal make-up, and that 1 (0.6 per cent.) showed the mental picture of an involutional psychosis.

From the above Table it will also be noted that in the 164 unselected cases of pellagra the disorders included in Group I constitute 95 per cent. (62 out of 65 cases) of the mental pictures observed in the series.

One is probably not justified in attempting to correct the groupings here given of the Georgia cases, because in many instances the patients were no longer in the hospital and the time available for a study of those remaining was very short. Nevertheless, it may be pointed out that the cases included under the head of "general paralytic type" seemed to be severe examples of delirium (none of these patients were seen) and that some of the manic-depressive depressions appeared to belong rather to our group of symptomatic depression. Of all the fifteen cases of dementia praecox type only four were still present in

TABLE 10.—TYPES OF MENTAL DISORDER ASSOCIATED WITH PELLAGRA ADMITTED TO THE GEORGIA STATE HOSPITAL IN 1911 AND 1912, TAKEN FROM THE ANNUAL REPORTS OF THAT INSTITUTION, AND OF THOSE ADMITTED TO THE SOUTH CAROLINA STATE HOSPITAL FROM SPARTANBURG COUNTY IN 1912 AND THE FIRST HALF OF 1913

	Georgia Cases				Columbia Cases				Per Cent. of Grand Total
	1911	1912	Total	Per Cent. of Total	1912	1913	Total	Per Cent. of Total	
Group I—									
Symptomatic depression..	0	0	0	0.0	2	1	3	10.3	1.7
Delirious pictures*.....	38	46	84	54.9	16	4	20	68.9	57.1
General paralytic type†...	6	2	8	5.2	0	0	0	0.0	4.4
Group II—									
Manic-depressive disorders	8	10	18	11.7	2	0	2	6.9	11.0
Dementia praecox disorders	9	6	15	9.8	2	1	3	10.3	9.9
Paranoic disorders.....	0	1	1	0.7	0	0	0	0.0	0.6
Group III—									
Involutional psychoses...	2	1	3	1.9	0	0	0	0.0	1.7
Senile dementia.....	2	0	2	1.3	1	0	1	3.4	1.7
Undetermined types.....	5	17	22	14.4	0	0	0	0.0	12.1
Total	70	83	153	100.0	23	6	29	100.0	100.0

*In the hospital reports these cases are grouped under the title of infective-exhaustive types.
†These in all probability belong with the delirious pictures.

July, 1913. In them the grouping seemed justifiable. Of the others, some were dead and the records at times suggested rather a delirious picture, while others had been discharged. A study of the records of the cases in which no type had been determined naturally permitted no conclusions, but it may be said that death followed speedily in many of the cases and this suggests that many of these patients belong in the delirious type.

Leaving the figures as given in the hospital reports it is obvious that delirium is by far the most frequent form of mental picture which leads to commitment. The effect of reclassification would be only to

augment this group at the expense of the others. It would be a matter of great value and interest if the subsequent history as regards outcome of the psychosis could be followed in detail for all cases in these various groups.

If one compares the proportion of the different groups in Table 10 with that in Table 9, it will be obvious that a very erroneous impression of the relative frequency of the different types of mental disorder associated with pellagra would be gained if the data were limited to the cases admitted to a hospital for the insane. Group I constitutes 95 per cent. of all forms in Table 9 and but 63 per cent. (as a minimum) in Table 10.

One other comparison may be made at this point which tends to emphasize the correlation between faulty nervous organization and liability to pellagra. According to the annual report of the Georgia State Sanitarium for 1912, there were admitted to that hospital 132 cases of dementia praecox and 150 cases of manic-depressive insanity. Among the pellagrins it will be seen from Table 10 that there were six examples of a dementia praecox type of personality, and ten of manic-depressive constitution. The ratio between pellagrous and non-pellagrous individuals in the two groups is 1 : 22 and 1 : 15, respectively, proportions which are unquestionably far greater than that of pellagrous to non-pellagrous sane inhabitants of the state of Georgia.

OUTCOME

From a practical point of view, this is probably the most important question of all. The facts recorded above afford ample justification for the general recognition of the frequent association between insanity and pellagra. But they do not support the gloomy prognostications which are so prevalent and so distressing in pellagrous regions.

It will be noted that of all the examples of mental disorder occurring in a series of 164 unselected cases, 95 per cent. are included under the heading of symptomatic depression or delirium. Furthermore, that of the cases committed as "insane" at least 63 per cent. come under this same category. All of these cases will recover provided they live through the attack of pellagra. The mental symptoms bear exactly the same relation to pellagra that the similar disturbances occurring in connection with other infective or intoxicative diseases, such as typhoid and tuberculosis, do to these diseases. They do not lead to any permanent mental disorganization.

This at once brings up the question as to whether there is any form of chronic insanity which can be considered as being directly due to pellagra. This question is necessarily closely bound up with the view which is taken as to the rôle which is played by pellagra in the etiology of dementia praecox. This has already been discussed and the view

expressed that such a development is the result of the personality of the individual rather than the consequence of the disease process which constitutes pellagra. Many of the examples of these types have shown definite mental disturbance prior to the outbreak of pellagra. It would be impossible to say definitely that all others would have developed the psychosis if they had not contracted pellagra, but there is no doubt in my mind that the probabilities are strongly in favor of such an occurrence. For, difficulties to be faced must occur in even the most protected existence and it becomes a question of the degree of ability possessed by the individual to adjust in a manner which more or less satisfactorily meets the difficulties. The answer to this question is the determining factor in the evolution of a psychosis. In other words, such a personality must be considered as always standing on the edge of a precipice over which he may slide as the result of any difficulty whatsoever, provided it cause him sufficiently to stumble. The man with average capacity for walking amid the irregularities of the pathway of life will successfully maintain his poise, while he with poorly balanced mechanisms of coordination or adaptation is liable to fall.

Besides this form of dementia, it is also possible that, like alcohol, pellagra might produce a degenerative condition in the nervous system with resulting chronic dementia. While this possibility cannot be denied, I can state definitely that in spite of a close search for examples of such end-result I have as yet failed to find one. At Milledgeville, an attempt was made to interview all still present patients with "psychoses accompanying pellagra," with this question in view, but without result. It may be that I am including some examples of this kind with the terminal stages of dementia praecox, but the number is certainly small and in my opinion entirely negligible.

It thus seems justifiable to conclude that pellagra is especially frequent in individuals of faulty nervous organization, and that in consequence there occur, in association with it, a greater percentage of such disorders as dementia praecox, manic-depressive insanity, hysteria, etc., than prevails among more healthy persons, yet the vast majority of the mental disturbances occurring in connection with pellagra are of no more significance *quâ* "insanity" than are the deliriums of typhoid fever. It is, however, probably true that, just as in that disease, the appearance of delirium or severe depression is a sign of the severity of intoxication and greater danger to life.

NERVOUS MANIFESTATIONS

This subject will be dealt with extremely briefly, for the reason that there is but little to add to what has already been said by me in the report of the Illinois Pellagra Commission. One cannot but be

impressed with the strong conviction which prevails that pellagra is especially a disease of the nervous system. Thus we find Wood[7] stating, "It is a daily problem with me and my colleagues to differentiate between myelitis of specific origin and similar pathologic conditions produced by pellagra."

Among the cases seen in the South, apart from the results of arteriosclerotic changes such as cerebral thromboses, it has been my experience to observe only one case in which there were evidences of chronic structural change in the nervous system. (This is entirely in keeping with the findings in regard to chronic dementia.) It is true that many of the severe and fatal cases present the syndrome of central neuritis, which is a reaction of the central nervous system to severe intoxication. This subject has already been amply discussed in the Illinois report and the anatomical findings in a series of cases published by L. J. Pollock and myself.[8] Dr. E. B. Saunders kindly furnished me with information as to the mode of death among pellagrins in the Columbia State Hospital. According to her observations, in a series of 88 fatal cases, sixty-four patients (74.7 per cent.) died with central neuritic symptoms, nineteen (21.6 per cent.) with appearances of simple exhaustion and five (5.6 per cent.) terminated suddenly from some unknown cause. In all severe cases there are evidences of irritable weakness in the nervous system, such as tremors, exaggeration of tendon-jerks, increased myotatic irritability, etc., entirely comparable to those met with in other severe intoxicative conditions, such as tuberculosis. Occasionally loss of knee-jerk is reported, the exact meaning of which is not always clear. The only example in the series here reported in which such a loss existed was that of an old man with severe arteriosclerosis who had suffered from a cerebral insult before the onset of the pellagra. The right knee-jerk (on the side of the hemiplegia) was present, but faint, while the left was absent. In the light of other experience, it seemed more probable that the lost knee-jerk was associated with some cerebral lesion rather than with the pellagra.

The single instance of chronic nervous disease which has come under my observation is deemed worthy of record in detail.

CASE 3.—*"Shut-in" type of personality. Loss of interest following first attack of pellagra. More definite psychosis of dementia praecox type of about nine months' duration ending in apparent recovery after a second attack of pellagra. Occasional sudden brief attacks of loss of power in the lower extremities since the first attack of pellagra. Atrophy of small muscles of hands and spastic paraplegia of gradual evolution following the second attack of pellagra.*

7. Wood, E. J.: Treatise on Pellagra, D. Appleton & Company, 1912, p. 228.
8. Singer, H. D., and Pollock, L. J.: The Histopathology of the Nervous System in Pellagra, THE ARCHIVES INT. MED., 1913, xi, 565.

F. B. M., white, male, aged 21, no occupation. Anamnesis obtained from the father, stepmother, sister and the patient. The mother died in all probability of pellagra seventeen years ago, although the diagnosis was not made at the time. Her illness is described as resembling in all particulars that of the patient as regards eruption on the hands, stomatitis and dysentery, except that it was more severe. The mother was nervous but there is no other history of importance.

The patient was always healthy and thought to be of average brightness. He had never been very enthusiastic about games and always preferred to play with children younger than himself. He was well liked, but had no confidants and kept much to himself; never cared to go out to parties, stayed much around home, and did not mix with members of the opposite sex. He was never a leader; did not read much and although he took pleasure in driving an automobile and caring for it, he seems to have spent much of his spare time loafing around the house. He has formed no definite plans or ambitions and seems to have taken it for granted that he will enter his father's business of lumber merchant. He has never caused any anxiety by getting into mischief and has been thought above the average in regard to morality. Thus the striking features of his make-up are chiefly negative and there is a lack of the push, activity and mischief of the average healthy boy.

In the summer of 1910 he suffered with an attack of malaria which was not very severe and from which he made a good recovery.

In March, 1911, there developed an erythema of the backs of the hands with some malaise which was recognized as *pellagra*. This attack was mild and disappeared in two or three weeks, but on his return to school it was noticed that he did not take as much interest as before. He wished to leave and fell behind so that his younger sister caught up and eventually passed him. He seemed to be unable to get his lessons, loafed around more and was even more retiring than formerly.

In the summer of 1911 he delivered papers for a newsdealer for a few days but then gave it up. While on his rounds he had a peculiar "spell" and had some ten or twelve of these between that time and October, 1912. As these attacks are said to be all alike it will suffice to describe one.

Spells: The onset is more or less abrupt and apparently most often during walking. The first manifestation is a sense of "drawing of the left side of the body," which seems to pull him over backwards and to the left. On some occasions he has been able to reach some support but generally he has fallen. His legs rapidly become stiff, weak and numb and for a while he cannot move them at all. There is no pain, dizziness or loss of consciousness according to the patient. The sister, however, stated that he had once been brought home unconscious in one of these spells. The patient recalls the incident and has apparently a clear recollection of it, so that it is at least doubtful whether he has ever lost consciousness. In an attack seen by the father he remained clear throughout. The paralysis gradually passes off and he is quite all right again in about fifteen to twenty minutes after the onset. In the attack observed by the father in June, 1912, while out in the woods he was able to walk back to camp at the end of twenty minutes, a distance of one and one-half miles.

There has never been any convulsive movement nor loss of sphincter control and he has seemed to recover fully afterwards.

In March, 1912, there was a second and more severe attack of *pellagra*. Following this he became listless, wanted to leave school and said that he could not keep his mind on his books. He did not seem depressed, but merely loafed on the porch or about the house. About the end of June he showed more definite evidence of insanity and began to express such notions as that everyone was watching them, the house was to be burned and they were to be shot. He did not react much to these thoughts and showed no sign of fear, but he did ask for his gun, which had been removed by his relatives, and once spoke to a policeman asking him to be on the watch for these people. He

wandered aimlessly about the house peering into corners and rummaging in drawers and had to be watched to prevent him from going away from the house. For a long time he carried a woolly rug around with him, offering no explanation for so doing. He seemed to take little notice of anything and was often very "obstinate." For a time he was entirely mute and refused food and medicine. He would object to getting into a bath and, once in, would refuse to come out, although he was never violent. Sense-falsifications were probably present. He would stop as if listening and mutter to himself and spoke of electricity and automobiles in his back.

He seems to have slowly become worse until October, 1912, when he was committed to the Columbia State Hospital. At this time it was noticed that he was weak in his legs and hands and required supporting to walk at all. This was, however, attributed to disuse and was not considered seriously.

It was impossible to determine the exact relation between the pellagra and the mental disturbance. The listlessness and loss of interest appeared in marked form soon after the appearance of the eruption on the hands, but this was entirely gone when he went to Columbia. It seemed probable that the diarrhea and stomatitis, which were present in March, had disappeared before July.

At Columbia the patient remained in bed with apparent indifference to his surroundings, but without active symptoms of any kind. Slowly he began to improve, both as regards interest in his environment and home, in his walking and the use of his hands, which were at first practically in abeyance. He was discharged as recovered July 17, 1913.

When examined the day after his return home the following facts were noted: A tall, muscular lad with an apparent age of not more than 17, although he was actually 21. There was little hair on the face, although it was normally present elsewhere on the body. The ears were large, irregular and asymmetrical. Genitalia well developed.

The gait was markedly spastic and he used a cane in walking. The feet showed a high arch. The knee- and ankle-jerks were markedly and equally exaggerated and a few clonic jerks, not sustained, were obtained at both ankles. Both plantar reflexes were of extensor type. The small muscles of the hands were much atrophied, with a characteristic *main en griffe*. The forearm muscles were small and power was much diminished, the wrists showing definite extension when an attempt was made to grip firmly. The grips were both feeble. No atrophy was detected elsewhere. Electrical examination was impossible owing to the lack of apparatus. The abdominal muscles were of good power and the epigastric and abdominal skin reflexes were present.

The only sensory disturbance discovered was a hypalgesia, not by any means complete, in the region of the first dorsal root distribution on the left forearm. No incoordination was detected.

A fine lateral nystagmus was present on extreme deviation of the eyes, especially when they were rotated to the left. No other ocular disturbances. Fundi healthy. The tongue deviated slightly towards the left when protruded, but there was no obvious loss of power in any movement and no defect in speech or swallowing. The facial movements were normal.

Bladder disturbance was at first entirely denied, but in reply to a leading question it was learned that there had developed some hesitation in starting the flow of urine.

The picture is thus not very clear or characteristic, but it was thought that the condition was probably one of syringomyelia and that the transient "attacks" of paraplegia might be due to minute hemorrhages or other vascular disturbance in the growth. Although it is said that he recovered perfectly from these attacks, it should be noted that the onset of the spasticity and atrophy of muscle were not noticed until they were severe and that the onset was quite possibly very insidious.

Katamnesis: With regard to the evidences of mental disorder, the patient simply denied most of them although he claimed to have been entirely clear

throughout. He admitted that he had been "out of his head" for the first period of his residence at Columbia, but attributed this to drugs and hypodermics. (The only drugs used were simple tonics.) He denied sense-falsifications except that he had had shocks "like electricity" in his back; denied that he had ever thought the house was to be burned or that people were watching the house. He would not meet or talk to people because he was afraid he might have one of his "attacks," of which he was ashamed. His memory for the events of the period of psychosis is apparently good and he gave a good account of his trip to Columbia.

He talked freely and answered questions without apparent evasion, but volunteered little and was not deeply concerned. His father considered him entirely recovered and attributed the somewhat listless attitude and poor interest to the weakness and disability resulting from the nervous lesion.

In spite of the close relation in point of time between the onset of the nervous symptoms and the attack of pellagra, one can hardly doubt that here the latter acted merely as a precipitating factor, both with regard to the psychosis and the nervous disease. As is well known, syringomyelic conditions are occasionally discovered at autopsy which have apparently caused no symptoms during life; also, it is not uncommon for the clinical manifestations to appear following some infectious fever in individuals who have previously been considered normal. The same is also true for other diseases belonging to this group of congenital anomaly, so that even if the suggestion that this is a case of syringomyelia is not correct the argument will still hold. The same explanation in all probability applies to the case published in England by Box[9] with a histological study by Mott.[10]

The occurrence of such cases as this is a further argument in favor of the suggestions which have been made in discussing the mental disorders, that faulty nervous organization seems for some reason to be associated with a predisposition to pellagra.

In closing this chapter reference may be made to the frequency with which manifestations appeared to point to especial involvement of the vestibular apparatus. This has been recorded before, but seemed to be especially prominent in the more severe forms of the disease observed in Spartanburg. Vertigo, often extremely annoying, at times constituted the main complaint of the patient. It was often sudden in onset and would result in falling, sometimes with vomiting. In most cases this dizziness would appear only when the patient was up and walking about, but in some it was present at times even when lying down. It was usually associated with more or less severe tinnitus and less frequently with a sense of pressure on the head. None of these attacks was actually observed. Among the eighteen severe cases in

9. Box, Charles R., and Mott, F. W.: Trans. Soc. Trop. Med. and Hyg., 1913, vi, 149; Brit. Med. Jour., July 5, 1913, p. 2.

10. Mott, F. W.: Trans. Soc. Trop. Med. and Hyg., 1913, vi, 157; Brit. Med. Jour., July 5, 1913, p. 4.

the Good Samaritan Hospital, this syndrome was more or less prominent in six.

SUMMARY AND CONCLUSIONS

1. Mental disturbance occurs in about 40 per cent. of all cases of pellagra. Such disturbances are more frequent with repeated attacks. Children are practically exempt. They are most common in men between 21 and 40, and women about 41 to 60.

2. About 95 per cent. of the mental disorders are the direct result of the pellagrous intoxication, and although the mortality in such cases is much higher than in cases without such disorder, yet the mental disturbance will fully recover if the patient survives. They correspond to similar disturbances in other somatic diseases and in such case are often described as not "insanity." The remaining 5 per cent. are examples of mental disorder primarily dependent on the individual's make-up, or else are merely concomitant.

3. Faulty nervous organization, including inadequate mental adaptability, seems to be associated with a predisposition to pellagra. This seems to afford the most satisfactory, even if only partial, explanation of the extraordinary frequency of pellagra arising among the insane, the increased frequency of functional psychoses and psychoneuroses and of nervous disease of the congenital anomaly type among pellagrins as compared with more normal individuals.

4. Chronic "insanity" due strictly to pellagrous intoxication, if it occurs, is rare.

5. Chronic nervous disease as the result of pellagra, if it occurs, is exceptional.

FURTHER OBSERVATIONS ON THE BLOOD-COUNT IN PELLAGRA*

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In a previous article[1] one of us summarized the more important changes that occur in the blood-count in pellagra. In the present communication we desire to record briefly our observations on another series of pellagrins, all of whom resided in, or adjacent to, Spartanburg County, South Carolina, in which locality the Thompson-McFadden Pellagra Commission has been investigating the disease. The data included in this report were obtained from patients examined during the summer and early fall months of 1913, when many new cases of pellagra were seen, as well as a large number of patients who had had one or more attacks of the disease. The information derived from this study confirms and amplifies the work of the commission carried on along the same lines in 1912. In the investigations of 1913 more particular attention was given to the relationship (if any) existing between the total leukocyte and differential counts, especially in the primary acute attacks of the disease. It was our main intention, however, to examine a fairly large and representative series of cases from the standpoint of the differential count, even in the absence of the correlated total leukocyte count. A few confirmatory observations were also made on the hemoglobin percentage and number of red corpuscles. The actual technic employed was essentially the same as detailed in the former paper, and was such as to insure consistent results with a minimal error.

In the accompanying table the differential leukocyte count is given on a series of forty-six pellagrins, together with the total leukocyte count when this was made, and also a few remarks with regard to the incidence of the attack, its nature (whether mild or severe), and the probable duration of the attack. Inspection of the table discloses the fact that lymphocytosis is the predominant feature in the majority of cases. In this connection it might be said that a few observations made on non-pellagrins in regions where pellagra was endemic revealed a moderate relative lymphocytosis, incidental, in all probability, to a poor state of general health, or to some mild gastro-intestinal disturbance.

* Submitted for publication July 18, 1914.

1. Hillman: Am. Jour. Med. Sc., 1913, cxiv, 507.

TABLE GIVING DATA CONCERNING BLOOD-COUNT OF PELLAGRINS

Name	Case No.	Sex	Age	Polynuclears	Lymphocytes	Large Monos.	Transitionals	Eosinophils	Basophils	Total Leukocytes	Nature and Duration of Attack
Q. J. F. ...	629	M	51	58.00	38.40	1.20	0.0	2.00	0.40	6,500	First attack, mild; six months.
D. W.	...	M	32	68.86	18.86	3.70	2.86	5.43	0.29	4,500	Recurrent attack, chronic; six months.
M. M.	628	F	30	72.80	18.60	1.60	1.40	5.40	0.20	10,000	First attack, severe; six weeks.
H. W.	518	F	40	49.75	46.25	2.50	1.00	0.50	0.0	6.050	First attack, severe, chronic; three months.
E. H.	...	F	38	64.20	29.40	1.40	0.80	4.20	0.0	7,200	Recurrent attack, chronic.
C. C. C. ..	582	M	43	78.75	16.25	2.25	2.50	0.25	0.0	6,000	Recurrent attack, chronic; two months.
S. J. H. ...	511	M	62	70.80	22.00	2.60	1.60	3.00	0.0	.....	Recurrent attack, chronic; four months, recovery.
S. M.	584	F	10	64.20	33.40	1.00	0.80	0.60	0.0	.....	Recurrent attack, chronic; three months, recovery.
E. S.	203	F	54	51.60	45.00	1.60	0.40	1.40	0.0	.....	Recurrent attack, chronic; six weeks, recovery.
S. R. M. ..	510	M	19	68.00	25.75	3.50	1.00	1.75	0.0	6,650	First attack, chronic; two months, recovery.
M. W. M.	688	M	52	53.40	38.40	3.20	0.60	4.40	0.0	8,800	First attack, chronic, two months.
B. S. A. ..	58	F	44	55.80	35.00	0.80	0.80	7.60	0.0	.....	Recurrent attack, chronic, mild, recovery.
E. S.	570	F	28	43.00	54.85	0.85	0.0	1.30	0.0	6,000	First attack, subacute; one month, recovery.
S.	500	M	48	62.75	32.50	0.50	0.25	3.00	0.0	8,200	Recurrent attack, chronic; one month, died.
S.	509	M	48	67.50	25.75	4.00	0.0	2.50	0.25	.....	Recurrent attack, chronic; died.
S. W. H. ..	553	M	22	68.25	25.00	1.00	0.00	5.50	0.25	.....	Recurrent attack, chronic; two months.
S. L.	76	F	35	58.80	36.00	0.80	0.40	2.00	0.0	7,500	Recurrent attack, chronic; recovery.
A. V.	500	M	13	65.00	30.25	1.50	1.00	2.00	0.25	.....	First attack, mild; recovery.
W. C. C. ..	701	M	32	59.25	31.25	3.75	2.00	2.75	1.00	.....	First attack, subacute; recovery.
C. D. E. ..	255	M	25	56.67	32.67	3.33	0.67	6.66	0.0	8,250	Recurrent attack, acute; two weeks.
F. L. T. ..	523	M	35	54.20	31.80	7.20	1.40	4.80	0.60	8,800	Recurrent attack, chronic.
T. M. P. ..	129	M	58	48.40	46.80	0.80	2.00	1.60	0.40	.....	First attack, chronic; mild, recovery.
C. M.	387	F	25	67.00	29.20	1.00	1.50	1.20	0.0	.....	Recurrent attack, acute; three weeks, died.
W. C. J. ..	526	M	49	73.80	22.00	1.00	2.00	1.20	0.0	7,150	First attack, acute; two weeks.
W. C. J. ..	526	M	49	38.00	59.30	1.10	0.60	1.00	0.0	6,700	First attack, subacute.
M. E. C. ..	516	M	48	52.50	39.00	2.50	0.0	4.50	1.50	6,000	Recurrent attack, acute; five weeks, died.
W. M.	528	F	12	53.60	34.20	1.80	1.40	8.80	0.20	8,800	First attack, chronic; five weeks, recovery..
R. W. C. .	502	M	56	73.00	18.90	4.50	2.00	1.10	0.50	8,750	Recurrent attack, chronic.
S.	506	F	20	70.00	24.00	2.00	1.00	2.60	0.40	.....	Recurrent attack, acute; died.
S. S .H. ..	144	F	35	51.20	37.80	2.60	3.00	5.00	0.40	.....	Recurrent attack, acute.
M. C. F. ..	...	F	17	59.00	33.40	2.20	2.20	2.80	0.40	10,150	First attack, acute; one week.
S.	634	M	35	55.00	43.00	1.33	0.67	0.0	0.0	9,800	First attack, acute; four weeks.
A. J. A. ...	505	M	35	45.70	49.30	2.40	0.30	2.30	0.0	7,550	Recurrent attack, acute.
S. E.	732	M	14	42.00	47.00	4.50	1.50	3.50	1.50	9,800	First attack, acute; four weeks.
B. J.	16	F	25	54.75	34.50	2.00	1.75	5.75	1.25	6,650	Recurrent attack, chronic; one month.
H. E.	...	F	35	61.25	33.50	2.75	1.00	1.00	0.50	.....	First attack, subacute; two months.
E. S.	206	F	54	45.50	49.00	0.50	1.50	3.00	0.50	.....	Recurrent attack, chronic.
W. R. G. ..	658	F	22	67.50	26.00	3.00	2.50	0.50	0.50	.....	Recurrent attack, subacute.
E. W.	549	M	10	50.50	43.50	2.00	0.25	3.50	0.25	9,800	First attack, acute; two weeks.
H. M.	708	F	45	69.75	22.50	3.00	1.00	2.75	0.0	8,000	Recurrent attack, chronic; mild.
R. L. L. ..	...	M	30	64.25	31.50	2.25	0.50	1.50	0.0	.....	First attack, acute; two weeks.
D. A.	552	F	24	61.50	32.75	3.25	1.25	1.25	0.0	.....	First attack, subacute; two months.
H. D.	572	F	32	42.00	57.00	0.50	0.0	0.25	0.25	8,000	Recurrent attack, chronic.
D.	575	F	53	51.00	40.50	5.50	1.0	1.25	0.75	6,500	First attack, chronic; mild.
G. E.	501	F	21	58.00	35.00	1.00	0.5	5.00	0.50	.....	First attack, chronic; two months.
E.	108	F	54	61.75	22.50	1.00	2.25	2.25	0.25	7,100	Recurrent, chronic; six weeks, severe.
Averages ..	...	..	35.5	58.87	34.57	2.23	1.12	2.86	0.25		

In cases showing a decided lymphocytosis, the total number of leukocytes was practically normal or only slightly below normal in a few instances. Marked and persistent leukopenia does not seem to be a feature of this disease. As far as we were able to determine from the cases studied, there appears to be no definite relation between the degree of lymphocytosis and the severity or chronicity of the attack. The small lymphocyte with relatively little cytoplasm is the most common type of lymphocyte in pellagrous blood.

In the few patients examined during the first stages of an acute attack, a tendency was noted toward a slight rise in the leukocytes to maximum normal or a trifle beyond, but in no instance was a pronounced leukocytosis found. The differential count on these cases did not exhibit a polynucleosis, and in only one case of acute severe pellagra were the polynuclears over 70 per cent. A rise in polynuclears was recorded in a few recurrent chronic cases, due most likely to complicating factors.

It has been mentioned by some workers on pellagra that the so-called large mononuclear leukocyte is relatively increased. Our observations would not tend to substantiate this finding as a constant feature, although in a few cases a slight rise in this type of cell was noted.

The eosinophils varied considerably, as may be seen from the table. A very moderate eosinophilia was found in occasional cases, but to state that eosinophilia is characteristic of pellagra would not be justified from a study of this analysis. The prevalence in the South of hookworm infection and other forms of intestinal parasitism capable of causing an eosinophilia, is a factor to be considered in interpreting slight fluctuations in the number of eosinophilic leukocytes.

With regard to the changes in the amount of hemoglobin and in the number of red corpuscles, it might be said that nothing further was detected other than a mild degree of secondary anemia which has been already noted in the first report. This anemia is not at all constant or characteristic of the disease. Cases of decided anemia occurred for the most part in patients afflicted with some associated condition to which the anemia was probably referable rather than to the pellagra *per se*.

STREPTOCOCCUS VIRIDANS IN ITS RELATION TO INFECTIONS OF THE UPPER RESPIRATORY TRACT *

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During the past decade numerous efforts have been made to devise a satisfactory classification of streptococci, most of them being based on the carbohydrate fermentation test. The most notable of the studies have been those of Gordon,[1] S. Andrewes and Horder,[2] Winslow,[3] and Floyd and Wolbach.[4] The reliability of the fermentation test has been questioned by Walker[5] and others. Schottmueller's[6] classification of streptococci, based on the appearance of the colonies on blood-agar, is at present perhaps the most practical, if not the most accurate classification of these bacteria. He divides them as follows:

1. *Streptococcus haemolyticus* (*longus, pyogenes*), which on blood-agar produces a clear zone of hemolysis about the colony; morphologically, it appears in chains of round or slightly oval cocci; this is the type almost constantly found in erysipelas, complications of scarlet fever and various suppurative processes of streptococcus origin.

2. *Streptococcus viridans* (*mitior*), which on blood-agar develops as a very small gray colony, surrounded by a zone of green; in smears the cocci are seen in pairs which resemble pneumococci, or in short and long chains of cocci, arranged in pairs. *Streptococcus viridans* is usually without capsule; it occurs chiefly in infections of endothelial and mucous surfaces.

3. *Streptococcus mucosus,* the colonies of which appear on blood-agar as delicate, colorless, transparent, glistening drops of a mucoid consistency; microscopically, it is composed of chains of diplococci, surrounded by a thick capsule which shows no indentation between the pairs.

Schottmueller's work has been followed by a number of similar studies in which the reaction on blood has been used as a basis for classification. Most of these investigators find that, clinically, the

* Submitted for publication July 16, 1914.
* From the Medical Clinic of the Presbyterian Hospital.
1. Gordon: Lancet, London, 1905, ii, 1400.
2. Andrewes and Horder: Lancet, London, 1906, clxxi, 708, 775, 852.
3. Winslow: Jour. Infect. Dis., 1912, x, 73.
4. Floyd and Wolbach: Jour. Med. Research, 1914, xxix, 493.
5. Walker: Jour. Path. and Bacteriol., 1910, xv.
6. Schottmueller: München. med. Wchnschr., 1903, li, 849, 909.

Streptococcus haemolyticus and *Streptococcus viridans* produce more or less characteristic lesions, the former being associated with suppurative or phlegmonous inflammation, the latter usually with milder catarrhal processes.

During the last two years I have been making a study of the bacteriology of infections of the upper respiratory tract, with special reference to the rôle played by *Streptococcus viridans* in these cases. The object of the investigation has been to determine:

1. The incidence of *Streptococcus viridans* in infections of the various parts of the upper air passages and their adnexa.

2. The clinical features of those infections in which *Streptococcus viridans* was the predominant organism.

3. The relation of such infections to arthritis, endocarditis and other systemic disorders.

4. The value of autogenous vaccines in their treatment and prevention.

More than a hundred cases have been studied, but for various reasons only eighty-nine have been included in the present report. The material for this study has been obtained for the most part from the medical clinic of the Presbyterian Hospital. A few cases from private practice have also been added.

TECHNIC

Without exception, the original cultures have been taken on glucose-blood-agar plates (in all cases human blood) defibrinated by sodium citrate or by shaking with glass beads. The agar was melted and one part of defibrinated blood added to two or three parts of agar. After the plates had hardened, the material to be examined was smeared over several of these (usually three) with sterile glass rods. This medium possesses the double advantage of being suitable for all the bacteria occurring in these parts and of furnishing a basis for the classification of streptococci according to Schottmueller's method. The differentiation of the green from the hemolytic colonies was much easier when the plates were a deep pink rather than red. This color was obtained by having the plates not too thick and by using blood slightly diluted with serum or salt solution. The blood used was always comparatively fresh and free from spontaneous hemolysis. It was found that blood which had remained in the ice-box for ten days or two weeks was unreliable. In old blood the cells become fragile and many strains of streptococci will produce hemolysis in it which fail to do so in fresh blood. In nearly every case smears were made at the time the cultures were taken and stained with methylene blue, Hiss' capsule stain and the Gram stain. The method of taking the

cultures will be described with each particular group of cases. A special effort was made in this study to determine the *predominating* organism; while pure cultures were rarely obtained, it was found that with careful technic one, or at most two, organisms usually far outnumbered any others that might be present and in so far as they predominated could be looked on as the probable exciting agents in the infection. In those few cases in which pure cultures were obtained there was no doubt as to the character of the infection. In the others, the presumption was, of course, in favor of the predominant organism, but one could no longer be sure that the infection was a pure one.

THE STREPTOCOCCUS VIRIDANS

Before proceeding to a consideration of the problems mentioned above, a brief description of the *Streptococcus viridans* might not be out of place. *Streptococcus viridans* in a typical form is a very small Gram-positive diplococcus which grows in pairs or short chains. The arrangement of the cocci in pairs is rather characteristic. It is usually described as having no capsule. The individual cocci are oblong and often definitely lanceolate. The chains are sometimes quite long, especially in liquid mediums, in which they may extend across the entire field of the microscope, but short chains are more typical. On glucose-blood-agar colonies on the surface develop slowly as minute round gray dots, with a narrow halo of green. If the blood-agar is thick and contains considerable blood, the colony takes on a brownish tinge. Deep colonies are round or fusiform and light green with darker centers. If old blood has been used, a certain amount of hemolysis may occur, but even then the green color survives. The pneumococcus also has a green colony on blood-agar, but it is larger and flatter, usually umbilicated and produces more green than the *Streptococcus viridans*. On plain or ascitic agar the *Streptococcus viridans* forms small gray colonies which may show (1) adherence to the medium and (2) considerable variations in size, so that one often suspects the culture of being contaminated. On ascitic agar there is occasionally some precipitation of the albumin, but never so marked as in the case of *Streptococcus haemolyticus*. The growth on ascitic agar is more luxuriant than on plain agar; on plain or ascitic broth there is usually produced a slight turbidity with a flocculent or granular sediment in the bottom of the tube; litmus milk is coagulated; inulin may or may not be coagulated, usually not. *Streptococcus viridans* is not soluble in bile or bile salts.

Variations.—The question as to whether the *Streptococcus viridans* is a pure type or merely an attenuated variant of the pneumococcus, is still an open question, with the evidence at present in favor of the

latter. The typical *Streptococcus viridans* is very small, but larger forms are often seen. The colony varies in size with that of the coccus. Short chains are more characteristic than long ones, but long chains do frequently occur. Small capsules are sometimes seen, in fresh smears particularly, after passage of the organism through animals. On culture mediums the variations are not marked. Strains are encountered which on the one hand approach the *Streptococcus haemolyticus,* forming no green and showing a slight tendency toward hemolysis; on the other hand, there are forms which resemble the pneumococcus, with colonies which are larger than that of the typical *Streptococcus viridans* and surrounded by a broader zone of green. In some cases the distinction from the pneumococcus is very hard to make. I have used the bile test as a final criterion. Inulin is fairly reliable, but there are a certain number of *Streptococcus viridans* cultures which will coagulate inulin. By repeated passage through animals Rosenow[7] was able to coagulate inulin with all his strains of *Streptococcus viridans.* He inferred from this and other mutations that the *Streptococcus viridans* was a modified pneumococcus. More recently Rosenow[8] has reported that by subjecting the organism to various modifications in environment he has succeeded in transmuting streptococci into typical pneumococci and vice versa. The significance of this work will be referred to later.

Virulence.—Streptococcus viridans is an organism of very low virulence for animals and rarely produces fatal infections in human beings. Of all the types in the streptococcus-pneumococcus group it approaches the nearest to being a saprophyte. This is particularly true of those growing in the normal buccal cavity. Davis[9] found that the typical *Streptococcus viridans* rarely produced arthritis in rabbits when injected intravenously. On the other hand, he and Rosenow[10] both found that experimental endocarditis could be produced in nearly every instance by inoculation with organisms of the *viridans* type. The organisms which Rosenow isolated from the joints in acute rheumatism he divided into three groups:

1. Diplococci which produce green on blood-agar.
2. Diplococci which produce slight hemolysis on blood-agar.
3. Diplococci which have no effect on blood-agar.

All these groups produce arthritis, endocarditis and pericarditis when injected into rabbits. The second group may also cause a myositis.

7. Rosenow, E. C.: Jour. Infect. Dis., 1910, vii, 411.
8. Rosenow, E. C.: Jour. Infect. Dis., 1914, xiv, 1.
9. Davis, D. J.: Jour. Infect. Dis., 1913, xii, 386.
10. Rosenow, E. C.: Jour. Infect. Dis., 1914, xiv, 61.

Immune Bodies.—Rosenow[7] has shown that the *Streptococcus viridans* produces specific agglutinins in chronic infectious endocarditis. The same investigator has studied the opsonins in chronic endocarditis of *Streptococcus viridans* origin. He has found that the opsonic index varies considerably at different periods of the disease and that embolism and other intercurrent processes in endocarditis are associated with a definite lowering of the destructive power of the patient's blood. Hastings[11] has recently employed complement-fixation tests for the diagnosis of *Streptococcus viridans* infections, particularly those of the joints. Rosenow and Davis have both succeeded in sensitizing guinea-pigs to *Streptococcus viridans*. Davis also found that animals sensitized to *Streptococcus haemolyticus* were not shocked by *Streptococcus viridans*.

Incidence of Streptococcus Viridans.—*Streptococcus viridans* has come to be associated in the minds of many almost exclusively with chronic infectious endocarditis. While it is the most frequent exciting agent in this disease, it should more properly be thought of as an inhabitant of the mouth and upper respiratory tract. It can be isolated from practically every normal mouth and throat. The importance of the streptococcus in infections of the upper respiratory tract has long been recognized, but comparatively little has been done to distinguish the various types from one another. *Streptococcus haemolyticus, Streptococcus viridans, Streptococcus mucosus* and the pneumococcus may all be found in healthy mouths, the *viridans* being usually the most abundant. In spite of this fact, however, most investigators of the bacteriology of the infections of the upper respiratory tract have been content to throw all streptococcus infections into one group, so that comparatively little is known of the relative importance of the different types in these infections. Schottmueller in his original article found *Streptococcus viridans* in tonsillitis, conjunctivitis, acute and chronic rhinitis, otitis media, empyema, pericarditis, lung abscess, endocarditis, acute enteritis and other abdominal inflammatory conditions; and recent studies of Camac,[12] Billings[13] and others on the relation of oral sepsis to chronic arthritis and the demonstration by Rosenow of *Streptococcus viridans* in the joints of rheumatic fever indicate what an important rôle this organism and its variants play in infections of the mucous and serous surfaces.

In the eighty-nine cases of infection of the upper respiratory tract which constitute the present bacteriological study, fifty, or 56.2 per

11. Hastings, T. W.: Jour. Exper. Med., 1914, xx, 52, 72.
12. Camac: Am. Jour. Med. Sc., 1914, cxlvii, 186.
13. Billings, Frank: Chronic Focal Infections and Their Etiologic Relations to Arthritis and Nephritis, THE ARCHIVES INT. MED., 1912, ix, 484.

cent., have shown a predominance of *Streptococcus viridans* on blood-agar plates. It seems rational in an investigation of this nature, in which, even with scrupulous technic, colonies of several species are often found on the plate, to attribute chief importance to the organism or organisms which are most largely represented. This is particularly true when the bacteria in question are hard to cultivate. For example, it would be much more significant if a plate showed 90 per cent. of its colonies to be *Bacillus influenzae* or *Streptococcus viridans,* than it would be if the plate were overgrown with *Bacillus proteus* or *Staphylococcus albus.* In the latter instance one would hesitate about making a positive bacteriological diagnosis, whereas in the former case, he could feel fairly sure that the specific organism had been discovered.

In the present study I have given especial attention to the *number* of colonies of each species present. My results therefore can hardly be compared with those of previous investigators who have usually set down merely the names of the organisms present without any reference to which were predominant.

By referring to the table of cases it will be seen that the *Streptococcus viridans* has been predominant in more than one-half of the cases studied. It has also been present, but not predominant, in a good many others. Next to the *Streptococcus viridans* in frequency comes the closely related pneumococcus which, including *Streptococcus mucosus,* was predominant in eighteen cases, or 20.2 per cent. of the series. The third in order of frequency was the *Streptococcus haemolyticus,* which was predominant in six cases (6.7 per cent.). These three organisms, therefore, were apparently the most active factor in about 83 per cent. of the cases studied. The remaining 17 per cent. was divided between Bacillus influenzae, *Micrococcus catarrhalis,* Friedländer's bacillus, Bacillus septus, *Staphylococcus aureus, Micrococcus paratetragenus,* and *Staphylococcus albus* and *citreus.* Bacillus coli and Bacillus proteus were never predominant. Some form of staphylococcus was encountered in almost every case, but only in a few instances was it predominant. The staphylococci appear to play a very insignificant rôle in infections of the upper respiratory tract.

STREPTOCOCCUS VIRIDANS IN INFECTIONS OF THE TONSILS

The streptococcus is by far the commonest micro-organism found in infected tonsils, both acute and chronic. This fact is so widely known that no reference to the literature is necessary. The distinction, however, between the *viridans* and other types of streptococci has not been usually made. Schottmueller,[6] Ruediger[14] and others have observed that the *Streptococcus haemolyticus* is usually found on the

14. Ruediger: Jour. Infect. Dis., 1906, iii, 755.

tonsils in scarlet fever. Streit,[15] in a recent study, found the *Streptococcus haemolyticus* in forty-nine out of fifty-six cases of tonsillitis and peritonsillar abscess. Davis[16] has recently studied the bacteriology of tonsillitis, particularly in relation to chronic rheumatic and renal disease. He examined extirpated tonsils from a large series of cases, mostly of arthritis, heart disease and chronic nephritis, and found that the *Streptococcus haemolyticus* was present in a large percentage of

Type of Infection	No. of Cases Studied	Strept. viridans Predominant	Other Organisms Predominant								
			Pneumococcus	Strept. haemolyt.	Strept. mucosus	Staph. aureus	Staph. albus	B. Influenzae	B. Friedlander	Micr. catarrh	B. septus
Acute tonsillitis	7	4	1	2	.....	.....	.....	....	.....	....	..
Acute tonsillitis associated with rheumatic fever	5	5	.....	.....	.....	.....	.....	....	.....	....	..
Chronic tonsillitis	5	2	1	1	.....	.....	1	....	.....	....	..
Chronic tonsillitis associated with infectious endocarditis	2	2	.....	.....	.....	.....	.....	....	.....	....	..
Chronic tonsillitis associated with chronic arthrit's	4	3	.....	1	.....	.....	.....	....	.....	....	..
Pyorrhea alveolaris	5	5	.....	.....	.....	.....	.....	....	.....	....	..
Alveolar abscess	2	2	.....	.....	.....	.....	.....	....	.....	....	..
Pyorrhea associated with acute arthritis	1	1	.....	.....	.....	.....	.....	....	.....	....	..
Pyorrhea associated with chronic arthritis	4	4	.....	.....	.....	.....	.....	....	.....	....	..
Pyorrhea associated with chronic nephitis	2	2	.....	.....	.....	.....	.....	....	.....	....	..
Alveolar abscess associated with infectious endocarditis	1	1	.....	.....	.....	.....	.....	....	.....	....	..
Acute coryza with pharyngitis	8	5	2	.....	.....	.....	.....	....	.....	....	1
Infections of the accessory sinuses	8	3	3	.....	.....	.....	.....	1	1	....	1
Infections of the ethmoid cells	4	.....	1	.....	.....	1	.....	....	1	....	..
Chronic daeryocystitis	1	1	.....	.....	.....	.....	.....	....	.....	....	..
Otitis media, acute	5	1	1	2	1	.....	.....	....	.....	....	..
Otitis media, chronic	2	.....	.....	.....	.....	2	.....	....	.....	....	..
Acute laryngitis	1	.....	1	.....	.....	.....	.....	....	.....	....	..
Acute bronchitis	8	4	3	.....	.....	.....	.....	1	.....	....	..
Chronic bronchitis	6	4	1	.....	.....	.....	.....	1	.....	....	..
Chronic pharyngitis	1	.....	1	.....	.....	.....	.....	....	.....	....	..
Chronic rhinitis	3	.....	.....	.....	.....	.....	.....	....	1	1	1
Normal throat	4	1	2	.....	.....	1	.....	....	.....	1	..
Total	89	50	17	6	1	3	1	3	3	2	3

them. In a few cases *Streptococcus viridans* was the predominant organism. His cultures were taken from deep in the tonsillar crypts. My own studies of the tonsillar flora have been confined to cultures taken from that organ in situ. Cultures were obtained as follows: The tonsil was wiped off with a sterile swab, and a sterile platinum

15. Streit: Arch. f. Laryngol. u. Rhinol., 1913, xxvii, 393.

16. Davis, D. J.: Bacteriological and Experimental Observations of Focal Infections, THE ARCHIVES INT. MED., 1912, ix, 505.

wire inserted as deep as possible into one of the crypts. The material removed was then spread over the surface of several blood-agar plates with a sterile glass rod. By this method colonies on the second or third plate were always sufficiently well separated for study. Smears were also made and stained in the usual way. The plates were examined after incubation at 37.5 C. (99.5 F.) for twenty-four hours and again after forty-eight hours, the predominating colony or colonies determined and the various types subcultured for further study.

I have examined the tonsils of twenty-three patients with more or less evidence of tonsillar disease. In sixteen of these *Streptococcus viridans* has been present in large numbers, sometimes in pure culture. In the remaining seven cases the pneumococcus or *Streptococcus haemolyticus* predominated, except in one instance in which *Staphylococcus albus* was found in almost pure culture.

Acute Tonsillitis.

The cases of tonsillitis, both acute and chronic, in which *Streptococcus viridans* has been the predominant organism, have been of a mild, or only moderately severe type. The *Streptococcus haemolyticus* is usually found with the tonsillitis of scarlet fever and peritonsillar abscess. I have seen several quite severe cases of tonsillitis from which pure cultures of the pneumococcus were obtained. Most cases of mild tonsillitis are probably due to *Streptococcus viridans*, but the clinical picture is certainly not characteristic enough to allow of a bacteriological diagnosis without a bacteriological examination.

It should be added that the smears made in these cases corresponded with the cultures, showing pus cells and diplococci in short chains.

In the one case of this group in which autogenous *Streptococcus viridans* vaccine was used the response was immediate. A tenacious membrane which had resisted local treatment for ten days disappeared within twenty-four hours after vaccination, and the patient made a rapid recovery.

Acute Tonsillitis Associated with Rheumatic Fever

In spite of the well-known association of tonsillitis with rheumatic fever, I know of no careful or extensive study of the bacteriology of the tonsil in this connection. My own series consists of only five cases. Cultures from the crypts of the tonsils in all of these showed *Streptococcus viridans* as the predominant organism. In one case it was present in pure growth.

Unfortunately, no cultures were made from the joints in any of these cases. Rosenow has recently cultivated from the joints in rheumatic fever streptococci which produce green on blood-agar and "after

prolonged cultivation come to resemble *Streptococcus viridans* in morphology, in cultural and pathogenic qualities." Rosenow's organism is probably identical with Poynton and Pane's[17] *Streptococcus rheumaticus*. In view of the widely accepted theory that the tonsil is the portal of entry for the organism of rheumatic fever, it is interesting to find that the *Streptococcus viridans* is so constantly present in the tonsils of these patients. Vaccines were not used in any of the cases. As they all responded well to salicylates, vaccine therapy was hardly indicated.

Streptococcus Viridans in Chronic Tonsillitis

The two cases of this character present nothing of particular interest except in indicating that *Streptococcus viridans* is a common finding in chronic hypertrophic tonsillitis.

Chronic Tonsillitis Associated with Infectious Endocarditis

The tonsils in these two very typical cases of subacute infectious endocarditis showed no external signs of disease, but cultures from the crypts gave practically pure growths of *Streptococcus viridans* and both patients gave histories of recent "colds," which may have been localized *Streptococcus viridans* infections of the nasopharynx and tonsils.

The strains of *Streptococcus viridans* obtained from the tonsils in these two cases reacted on culture mediums in the same way as those recovered from the blood. Morphologically, however, the cocci from the tonsils were somewhat larger than those from the blood.

Autogenous vaccines, both the killed and the sensitized living, were administered in both these cases. At times the vaccine seemed to reduce the temperature, but the effect was only temporary.

Chronic Tonsillitis Associated with Chronic Arthritis

There were three cases of this character in which *Streptococcus viridans* predominated in cultures from the tonsil. In these three cases the existence of tonsillar disease was quite evident. In every instance smears from the tonsillar crypts showed pus cells in addition to Gram-positive diplococci. In the first case, the tonsils were removed and autogenous vaccine administered, and the patient's joints began to improve immediately. In the other two the tonsils were not removed and the condition of the patients remained unchanged, though one of them received large doses of autogenous vaccine. The first case was much less advanced than the other two, and hence was more amenable to treatment. This patient eventually made a complete recovery.

17. Poynton and Pane: Lancet, London, 1900, ii, 861; ibid., 1910, i, 152, 1528.

Two of the cases in this series illustrate a condition which I have observed several times, namely, the combination of both pyorrhea and tonsillitis with arthritis.

STREPTOCOCCUS VIRIDANS IN INFECTION OF THE ALVEOLAR SOCKETS (PYORRHEA ALVEOLARIS; ALVEOLAR ABSCESS)

The only extensive study of the bacteriology of pyorrhea is that of Goadby,[18] who in ninety cases, found the streptococcus in fifty-five and the staphylococcus in sixty-three of them. His cultures were taken on slant agar. No one organism has ever been held responsible for pyorrhea, but Ankovy[19] thought that the disease was probably of streptococcic origin. In the more recent studies of oral sepsis and its relation to systemic disease, some form of streptococcus has usually been found present, often in association with Bacillus fusiformis and spirochetes. My own series comprises 15 cases.

Technic of Taking Cultures

Before taking the cultures the teeth were subjected to a thorough cleansing by a dentist. If this was not possible, a nurse scrubbed the teeth and gums well with potassium chlorate. When the culture was to be taken the gum was rubbed off with alcohol, dried with a sterile gauze sponge and a drop of pus squeezed out. A loopful was then transferred to blood-agar plates, and another loopful smeared on glass slides.

From all of the fifteen cases studied an abundant growth of *Streptococcus viridans* was obtained, in some cases practically pure.

Pyorrhea is exceedingly common among the lower classes and is frequent enough in all classes. Filthy teeth, the gouty diathesis, improper bridge-work, etc., are important predisposing causes. The infection is usually secondary, developing after the gum and root membrane have been subjected to chemical or mechanical injury. Autogenous vaccines have been beneficial in some cases. In one case of the present series an autogenous *Streptococcus viridans* vaccine eliminated that organism from the discharge and produced considerable diminution in its amount. Smears, however, showed the persistance of large numbers of spirochetes. Anaerobic cultures were now taken on Noguchi's ascitic agar medium and a pure growth of *Treponema microdentium* was obtained. A vaccine was prepared from this organism, and two inoculations were given. The patient then went abroad and the treatment was never resumed. Pyorrhea in most cases remains a purely local infection, but there is considerable

18. Goadby: Lancet, London, 1907, i, 632.
19. Ankovy: Quoted by Goadby, reference not given.

evidence to show that in some instances it is responsible for certain systemic disorders.

Streptococcus Viridans in Infection of the Alveolar Sockets Associated with Acute Arthritis.—There was only one case of this type, an acute polyarthritis of the rheumatic fever type, associated with marked pyorrhea. In the absence of any other local lesion in this case one is led to suspect that the infected tooth sockets were the foci from which the joints were infected. It is unfortunate that in this case no cultures were taken from the joints. Cultures taken according to Rosenow's technic might have given positive results.

Streptococcus Viridans in Infection of the Alveolar Sockets Associated with Chronic Arthritis.—There were four cases of this character in which *Streptococcus viridans* was the predominant organism in the cultures from the tonsillar crypts. These cases are of a type that is being recognized more and more frequently. Just how responsible pyorrhea is for the joint changes in chronic arthritis it is at present impossible to say. Rosenow[20] has recently been able to cultivate a streptococcus closely resembling the *viridans* from lymph-glands adjacent to such joints, a fact which would suggest a rather close connection. Certainly many of these cases improve when the condition in the mouth is corrected. This is particularly true in the earlier cases, in which bony changes have not yet occurred. In two out of the four cases just reported there was improvement after the pyorrhea had received attention and autogenous vaccines had been given. One case has not been heard from. This case, by the way, afforded another instance of the association of tonsillitis with pyorrhea.

Streptococcus Viridans in Infection of the Alveolar Sockets Associated with Chronic Nephritis.—The occasional association of nephritis with tonsillitis has long been recognized, but little attention has been paid to pyorrhea as an etiological factor in disease of the kidney. I have studied the bacteriology in two cases of pyorrhea associated with chronic nephritis. In both of them *Streptococcus viridans* was the predominant organism. One of the cases was particularly interesting in that the patient had a high temperature and showed many petechiae on the body. Under the usual treatment, which was augmented with dental hygiene and an autogenous vaccine, the temperature returned to normal and the patient made considerable improvement.

Streptococcus Viridans in Infection of the Alveolar Socket Associated with Chronic Infectious Endocarditis.—This was a typical case of infectious endocarditis and needs no comment further than to say

20. Rosenow, E. C.: Etiology of Arthritis Deformans, Jour. Am. Med. Assn., 1914, lxii, 1146.

that if the alveolar abscess had been discovered in time, the patient would probably never have developed endocarditis. The streptococcus obtained from the abscess was practically identical with that found in the blood, the only difference being that the former was a little larger in size.

STREPTOCOCCUS VIRIDANS IN INFECTION OF THE PHARYNX AND THE NASAL CAVITIES

The bacteriology of coryza has been extensively studied, but in spite of this there still remains considerable disagreement and doubt on the subject. Cultures from coryzas in the acute stage are often sterile, while in cultures taken in the subacute or chronic stage, there are often several types present, so that it is difficult to decide which organism is the causative factor.

Various bacteria have been considered as more or less specific for colds. Cautley[21] in 1894 described a small bacillus, since known as *Bacillus septus*, which he considered the exciting agent in the majority of colds. White[22] and Walter[23] have also attributed considerable importance to *Bacillus septus* in the etiology of colds. Recently, Tunnicliff[24] has described a small spirochete which she has been able to isolate from acute and chronic coryzas. Allen[25] makes the statement that the streptococcus is the most frequent cause of "purulent nasal catarrh," referring doubtless to subacute and chronic coryzas. Numerous writers have shown that the normal nasal cavity is sterile or practically so. Hasslauer[26] studied seventy-eight cases of nasal catarrh and found that in acute cases streptococcus, pneumococcus and the pseudodiphtheria bacillus were most numerous and most frequently found. Schottmueller,[6] in his original study of *Streptococcus viridans*, frequently found this organism almost pure in acute and chronic rhinitis.

The *Streptococcus viridans*, like the pneumococcus, is an inhabitant of the normal mouth. It is usually easy to isolate it on plates from any healthy pharynx.

Acute Coryza with Pharyngitis

I have studied only a limited number of coryzas, eight in all. In taking cultures from the nose, the vestibules were first cleaned out with soap and water, and then a plug of absorbent cotton soaked with

21. Cautley: Ann. Rep. Local Govt. Bd. Med. Suppl., 1894-1895, xxiv, 455.
22. White: Catarrhal Fevers, London, 1906, p. 54.
23. Walter: A Study of the Bacterial Flora of the Nasal Mucosa in the Presence of Rhinitis, Jour. Am. Med. Assn., 1910, lv, 1091.
24. Tunnicliff: Jour. Infect. Dis., 1913, xiii, 283.
25. Allen: Brit. Med. Jour., 1906, ii, 721; Lancet, London, 1908, ii, 1589, 1659.
26. Hasslauer: Centralbl. f. Bakteriol., 1902, xxxiii, 47.

95 per cent. alcohol was inserted in each nostril and allowed to remain there several minutes. When the plugs had been removed a sterile nasal speculum was inserted and several loops of secretion from the middle meatus were carefully removed with a platinum wire and smeared over the plates. In some cases the patient was asked to blow on a piece of sterile gauze. Some of the secretion was then washed with sterile saline and plated in the usual manner.

Cultures from the pharynx were taken with a sterile swab, after the throat had been well gargled with sterile salt solution.

Of the eight cases so studied, five gave evidence of being of *Streptococcus viridans* origin.

Streptococcus viridans coryzas frequently start in the throat and extend upward or downward, or both. They show a distinct tendency to recur. This was very noticeable in two of the cases. In view of the close relation of *Streptococcus viridans* to the pneumococcus, it is noteworthy that in two cases the patients had previously suffered from pneumococcus infections. In one case autogenous *Streptococcus viridans* vaccine was given a thorough trial and proved most effective in protecting the patient against subsequent infection. The inoculations were started in January and were repeated once a week through the remainder of the winter and early spring.

STREPTOCOCCUS VIRIDANS IN INFECTION OF THE ACCESSORY SINUSES

It has been shown by Toerne[27] that healthy sinuses are practically always free from bacteria. Herzfeld and Hermann[28] studied the bacteria in ten cases of antral empyema and found non-virulent streptococci (probably *viridans*) in eight of them. In six cases the streptococcus either was present in pure culture or was noted as the predominant species. Howard and Ingersoll,[29] in eighteen cases of sinus infection, obtained the streptococcus in half of them (four times in pure culture) and the pneumococcus in four. Lichtwitz,[30] in a study of sinus infections, concludes that the streptococcus and staphylococcus are responsible for most sinus infections. Stanculeanu and Baup[31] divide facial empyema into two groups: first, the fetid type, in which infection takes place through the teeth; anaerobes are usually most active in these; and second, non-fetid types, infection through the nose, usually due to streptococcus or pneumococcus. Lewis and Turner's[32]

27. Toerne: Centralbl. f. Bakteriol., 1903, xxxiii, 250.
28. Herzfeld and Hermann: Arch. f. Laryng. u. Rhinol., 1895, iii, 143.
29. Howard and Ingersoll: Am. Jour. Med. Sc., 1898, cxv, 520.
30. Lichtwitz: Prag. med. Wchnschr., 1894, 31.
31. Stanculeanu and Baup: Arch. de Sc. méd., 1900, v, 121.
32. Lewis and Turner: Edinburgh Med. Jour., 1905, ii, 393.

study of the bacteriology of sinus infection covers seventy-four cases. In the acute cases, streptococci were present in 60 per cent.; in the chronic cases in 80 per cent. The pneumococcus was found in almost as large a percentage. Allen's[33] results in thirty cases of sinusitis differ from previous studies in showing a high incidence of *Bacillus influenzae* (73 per cent.). The streptococcus or pneumococcus or both, were present, however, in 80 per cent. of the cases also.

I have studied the flora in eight cases of sinus infection. The cultures were obtained under strict bacteriological technic. In all but one of the cases I was assisted by a laryngologist who aspirated the pus from the sinus with sterile instruments.

In three cases I found the *Streptococcus viridans* predominant. One was an antrum infection, another frontal, and in the third, both were involved. In the last, the patient suffered from severe attacks of bronchial asthma.

It is often difficult to cultivate the *Streptococcus viridans* from the sinuses, even when the organisms can be seen in smears. This was my experience in two cases, in which repeated cultures were sterile. This is particularly liable to occur if the pus has been allowed to remain for several days in the sinus. Freshly secreted pus is much more likely to give a growth than old pus in which presumably the bacteria have been destroyed by bactericidal substances.

Chronic sinus infections of whatever origin do not yield readily to vaccine treatment or to any other form of treatment. One of my patients was considerably relieved from frontal headache by large doses of autogenous *Streptococcus viridans* vaccine. The discharge was diminished, but did not entirely disappear.

In one case of sinusitis associated with asthma there was considerable sensitiveness to *Streptococcus viridans* vaccine. An injection of 100 million produced within five hours a very marked general reaction which lasted twenty-four hours. There were general malaise, fever and increased secretion from the sinuses. Fortunately, this sensitiveness has now disappeared, so that he is able to take doses of 2 billion or more without trouble. The asthma has improved, but the sinuses remain about the same.

STREPTOCOCCUS VIRIDANS IN INFECTION OF TEAR SAC (CHRONIC DACRYOCYSTITIS)

I have studied the bacteriology of only one case of dacryocystitis, and this proved to be a pure infection of *Streptococcus viridans*. Removal of the sac resulted in complete cure.

33. Allen: Bacterial Diseases of Respiration, Philadelphia, 1913, p. 53.

STREPTOCOCCUS VIRIDANS IN INFECTION OF THE MIDDLE EAR

Streptococcus viridans infections of the middle ear are unusual. *Streptococcus haemolyticus* or *mucosus*, or the pneumococcus are more frequently found in the acute cases, and *Staphylococcus aureus* or *albus* in the chronic. Out of seven cases studied, I have encountered only one of *Streptococcus viridans* otitis. This was in a boy 5 years old. The infection ran a short, mild course, and the mastoid was not involved.

STREPTOCOCCUS VIRIDANS IN INFECTION OF THE TRACHEA AND BRONCHI

The bacteriology of bronchitis has been studied thoroughly by many observers, but most of these studies were made before blood-agar mediums came into general use. I have not investigated the literature earlier than 1900, but since that time there have been a number of careful studies of the subject. Marfan[34] found that the streptococcus and pneumococcus were the organisms most frequently found in bronchitis. Forscheimer[35] noted that the streptococcus always replaced the influenza bacillus in influenza bronchitis. Babes and Beldiman,[36] and Bartel[37] have emphasized the importance of streptococcus and pneumococcus in bronchitis. Pollak[38] in 1908 studied 73 cases of purulent bronchitis at necropsy and found the pneumococcus 41 times; the streptococcus 27 times, and the *Staphylococcus aureus* 31 times. Other bacteria were much less frequent.

Ritchie[39] examined the bacteria in 49 cases of bronchitis with the following results: Streptococcus was present in 34 cases (70 per cent.), pneumococcus in 46.9 per cent. He concludes that "these two are certainly the most important causal bacteria in bronchitis." Hastings and Niles[40] have recently studied the bacteriology of bronchitis and pneumonia and have found streptococcus, pneumococcus and *Micrococcus catarrhalis* the most frequent invaders. Holt's[41] results in 354 cultures from bronchitis in children are interesting. The pneumococcus

34. Marfan: Traité de médecine, 1901, vi, 281.
35. Forscheimer: Med. News, 1901, lxxviii, 851.
36. Babes and Beldiman: Ann. de l'Inst. de path. et de bact. de Bucarest, 1894, 145.
37. Bartel: Centralbl. f. Bakteriol., 1898, xxiv, Part 1, p. 401.
38. Pollak: Wien. klin. Wchnschr., 1908, xxi, 973.
39. Ritchie: Jour. Path. and Bacteriol., 1901, vii, 1.
40. Hastings and Niles: Jour. Exper. Med., 1911, xiii, 638.
41. Holt, L. E.: The Bacteriology of Acute Infections of the Respiratory Tract in Children, with Especial reference to Influenza, THE ARCHIVES INT. MED., 1910, v, 449; The Bacteriology of Acute Respiratory Infections in Children as Determined by Cultures from the Bronchial Secretion, Jour. Am. Med. Assn., 1910, lv, 1241.

was present in 231 cases, the streptococcus in 109, and the *Staphylococcus aureus* in 266. In none of these studies has the distinction between the *Streptococcus viridans* and *Streptococcus haemolyticus* been brought out.

During the past two years I have studied the sputum from fourteen cases of bronchitis (acute and chronic). In eight of these the *Streptococcus viridans* was predominant or present in pure culture. Kitasato's method was used in making the examinations. Freshly expectorated sputum was washed several times with salt solution, then a small portion was removed from the center of one of the masses and smeared over blood-agar plates.

Acute Bronchitis.—Acute bronchitis of *Streptococcus viridans* origin is usually mild, as all other infections with this organism tend to be. Three out of the four cases studied were subject to repeated acute attacks, again illustrating the failure of the body to develop a permanent immunity against this organism. Only one of these patients was vaccinated against *Streptococcus viridans*. Case 4 received autogenous vaccine every five to seven days through the late winter and spring, and has had no more infections of any kind since the vaccine treatment has been instituted.

Chronic Bronchitis.—Four of the six chronic bronchitis cases showed a predominance of *Streptococcus viridans* in the sputum. When I compared these four cases I was surprised to find that they all had with their cough more or less well-defined asthma. This is probably a coincidence, but agrees with the work of Allen, who found streptococci in the sputum of practically all asthmatics. In the first two cases the asthmatic symptoms were quite typical. The second case had in addition a quiescent tuberculous process. According to Allen, there are some cases of asthma in which vaccine is of benefit. It was employed in only one of this series. Autogenous vaccine was given through the entire winter and by this means the cough was kept well in control. When the vaccine was omitted for any length of time, however, the symptoms recurred.

CLINICAL COURSE

If one studies the general clinical course of *Streptococcus viridans* infection of the upper respiratory tract, they are seen to have three very definite characteristics:

1. They usually run a mild course. The *Streptococcus viridans* is essentially a germ of low virulence for animals and man alike. In the present series of cases the severe infections have nearly always been caused by the pneumococcus or the *Streptococcus haemolyticus*.

2. They have a tendency to become chronic. This applies particularly to pyorrhea, tonsillitis and sinusitis. *Streptococcus viridans* bronchitis and rhinitis often run a chronic course also.

3. They are followed by little or no immunity and are therefore quite prone to recur at frequent intervals. This trait, well illustrated in the coryza and bronchitis series, follows from the low virulence which the organism possesses. Its metabolism disturbs the body so little that only a small amount of protective substance is developed against it.

The present study gives some weight to the idea that *Streptococcus viridans* infections play an important part in the etiology of certain systemic diseases, especially arthritis, endocarditis and nephritis. *Streptococcus viridans* can usually be isolated from the crypts of the tonsil in acute rheumatism. Rosenow has cultivated streptococci from the joints in acute rheumatism, and has found that except for slight variations they differ in no way from *Streptococcus viridans*. Davis found *Streptococcus haemolyticus* more commonly in the tonsils of chronic arthritis and nephritis, but, in my own experience, the *viridans* is just as frequently found in these diseases.

It is noteworthy that of all the *Streptococcus viridans* infections of the upper respiratory tract, it is almost exclusively those of the tonsils and tooth sockets (occasionally of the sinuses) that are associated with systemic disease. Rosenow's studies on the transmutation of streptococci and pneumococci are interesting in this connection. To quote Rosenow:

> The fact that variations in oxygen tensions and salt concentration, that growth in symbiosis with other bacteria and that injections into cavities in animals commonly call forth mutational forms in streptococci suggests strongly that similar changes might occur in various foci of infection where such conditions may prevail. It would seem therefore that focal infections are no longer to be looked upon merely as a place of entrance of bacteria but as a place where conditions are favorable for them to acquire the properties which give them a wide range of affinities for various structures.

The places in the human body where such conditions prevail are apparently the tonsils, sinuses and tooth sockets. By this reasoning can be explained the slight differences which have been noted between the strain of streptococcus isolated from the mouth and that obtained from the heart valve or joint.

VALUE OF VACCINES

There remains to be considered the value of vaccines in the treatment and prevention of *Streptococcus viridans* infections. As a result of the present study I feel no hesitancy in saying that autogenous vaccine may be of great value in selected cases of subacute and chronic

infection by this organism. Naturally, in those cases in which the infection is accompanied by extensive structural changes, as, for example, bronchitis with emphysema or bronchiectasis, old sinus infections with thickened walls, advanced pyorrhea with retraction of the gums, and tonsillitis with hypertrophy, the benefit which a vaccine can bestow is limited.

It is in the prevention of recurrences of these infections that vaccine is most valuable. In several cases of my series, patients who had been subject to frequent reinfections were successfully carried by means of vaccination through the winter and spring without any further recurrence of these troubles.

Prophylactic vaccination against infections of the upper respiratory tract is a matter which deserves more study. It is rather strange that prophylactic vaccination of dogs against distemper should be so generally in use, while so little effort is being made to protect human beings against coughs and colds. From my own experience, I should favor the view that most persons who suffer from frequent colds are susceptible to one particular organism with which they are constantly being reinfected. Moreover, the more carefully one studies these cases, the less weight he attaches to the idea of their being usually mixed infections. It is probably one organism that causes the infection in most cases. The others, being present on the infected surface, multiply in the rich secretions which are poured out, and simply serve to confuse the bacteriological picture. If this is the case there is all the more reason why every effort should be made to discover the offending organism, and if necessary to protect the patient against further infection.

SUMMARY

1. In a bacteriological study of eighty-nine infections of the upper respiratory tract, the *Streptococcus viridans* has been the predominant organism in fifty cases, or 56.2 per cent. If the cases in which the pneumococcus or *Streptococcus haemolyticus* were predominant be added to this group, it can be said that in 85 per cent. of the cases studied, one or the other of these closely allied species was apparently concerned in the infection.

2. *Streptococcus viridans* infections of the upper respiratory tract are characterized by their mild course and a tendency to chronicity and frequent recurrences, owing in great measure to the short duration of the acquired immunity.

3. *Streptococcus viridans* infections of the upper respiratory tract, especially those of the tonsils, sinuses and alveolar sockets, are frequently associated with endocarditis and arthritis. In these cases there

is much evidence in favor of the theory that the infections of the serous membranes are secondary to the infections of the upper air passages.

4. Autogenous *Streptococcus viridans* vaccines are of considerable value in cases in which structural changes are not too advanced. Their administration may also be useful in the prevention of recurrences.

123 East Sixty-second Street.

A CASE OF INDEPENDENT VENTRICULAR ACTIVITY OCCURRING DURING ACUTE ARTICULAR RHEUMATISM *

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History.—S. P., male, aged 20, entered the Har Moriah Hospital, Feb. 4, 1913. He had measles when 3 years old and typhoid when 10; otherwise there was no history of any previous illness. He was not addicted to tea, coffee, tobacco or alcohol. Five days before admission he developed a typical attack of acute articular rheumatism involving the ankles, wrists, knees and elbows. The attack was accompanied by fever; there were no chills or gastric disturbances.

On admission, except for swelling and redness of the inflamed joints, the physical and neurological examination revealed nothing abnormal. There was no urethral discharge. The complement-fixation test for gonococci was negative. The cardiac outline was normal to percussion, the apex beat was in the fifth interspace, 8.5 cm. from the midsternal line; the heart sounds were normal; the pulse was rhythmical. The systolic and diastolic blood-pressures were within normal limits. The temperature ranged between 101 and 103. There was no dyspnea. The patient did not appear very ill; sodium salicylate in moderate doses was given for two days.

Two days after admission a transient pulse irregularity appeared. Six days thereafter, it recurred once in about fifteen beats and clinically resembled extrasystoles; no tracings were made at that time. February 12, the irregularity occurred every third or fourth beat. From that day frequent polygraphic and later electrocardiographic tracings were taken. February 14, for the first time a rough blowing systolic murmur was heard at the apex. Occasionally there were runs of from three to twelve stronger thumping beats accompanied by the murmur; studies of the tracings showed that these beats were due to simultaneous action of auricle and ventricle. Four days later the arhythmia was very infrequent, the systolic murmur had almost entirely disappeared. The patient left the hospital feeling well.

Polygraphic and Electrocardiographic Tracings.—In Figure 1, *a*, *b*, *c* are continuous parts of polygraphic tracings taken February 12. In Figure 1 *a*, with the exception of three rhythmic beats (5, 6, 7 in the venous curve of Figure 1 *a*) independent ventricular action is present, as is evidenced by the carotid wave, *c*, falling with or preceding the auricular wave, *a*; one ventricular extrasystole (r') is also present. Figure 1 *b* shows a similar arhythmia with varying *c-a* intervals and occasional simultaneous action of auricle and ventricle. The rhythm again becomes normal in the last section of the tracing (Fig. 1 *c* at *n*). The average pulse-rate throughout is sixty per minute, though the beats which inaugurate the normal rhythm (Figure 1 *c*, X′ and X″) are somewhat more rapid. The entire tracing is typical of those taken on the days when the arhythmia was marked (for instance, Fig. 2, *a* and *b*). One week later the pulse was rhythmical except for an occasional independent ventricular contraction (Fig. 3 at *I*), the rate about 57 per minute. February 26, the rhythm was normal, the rate 70. Subsequently, pressure on the vagi was practiced to study its effect on the rhythm. Left vagus pressure showed a transient increase of pulse rapidity (Fig. 4). During right vagus pressure (Fig. 5) there was slight temporary slowing of the pulse-rate. Neither right nor left vagus pressure had any effect on the normal auriculoventricular sequence. After sufficient time

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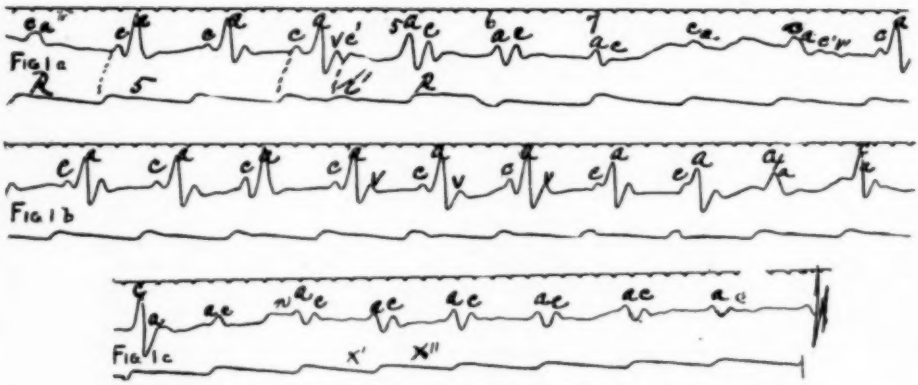

Fig. 1.—Continuous polygraphic tracing taken February 12. In Figure 1 *a*, except beats 5, 6 and 7 (venous tracing), independent ventricular beats are present; the carotid wave, *c*, precedes or falls with the auricular wave, a. R = radial pulse; r′ = ventricular extrasystole. Average pulse-rate is 60 per minute. In Figure 1 *b*, ventricular automatism with varying *c-a* intervals and occasional simultaneous action of auricle and ventricle (superposition of *a* and *c*) are present. Figure 1 *c*, rhythm becomes normal at *n*. X′ and X″ and somewhat more rapid beats which inaugurate the normal rhythm.

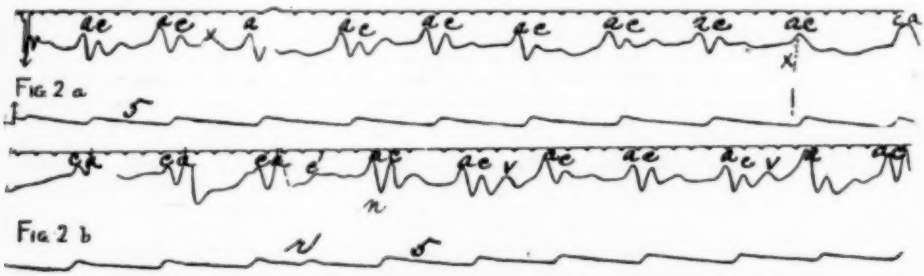

Fig. 2.—Continuous tracing taken February 13. The automatic beats begin at X. The rhythm is again normal at *n* (Fig. 2 *b*). The numerals on the radial beats represent their lengths in fifths of a second. Except for extrasystole (r′) the rhythm has been normal, the rate 60 per minute.

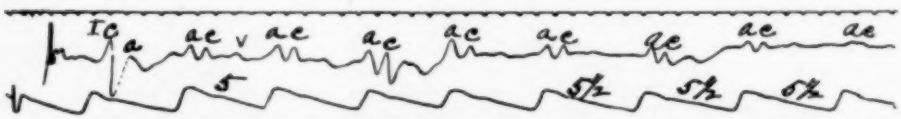

Fig. 3.—Section of a long polygraphic tracing taken February 19. It shows one independent ventricular contraction at I.

had been allowed for the heart to recover from vagus pressure, atropin sulphate, 1/30 grain, was injected subcutaneously and a continuous polygraphic tracing lasting one hour was taken, the important sections of which are reproduced (Fig. 6, *a* and *b*). They show that ten minutes after the injection ventricular automatism was occasionally present; the rate throughout was 60 per minute. Immediately preceding this arhythmia, the rhythm had been normal with an occasional increase of rate to 75 per minute. At the end of the atropin experiment the pulse-rate was 100, the beats sequential.

Many electrocardiograms were taken, two of which are given (Figs. 7 and 8). The rhythm is normal in the first lead (Figure 7, *a*). In the first section of

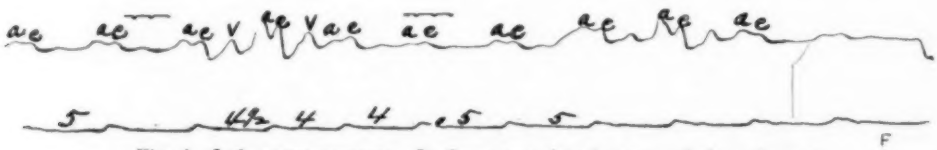

Fig. 4.—Left vagus pressure. It shows transient increase of the pulse-rate. The venous curve is somewhat distorted by the digital pressure on the vein.

Fig. 5.—Right vagus pressure. It shows slight transient slowing of the pulse-rate; later the rate increased.

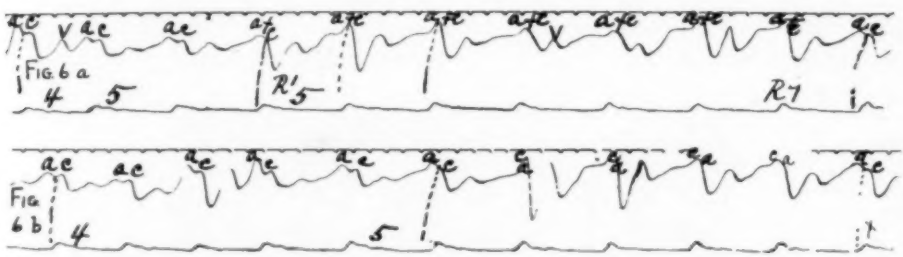

Fig. 6 *a*.—Ten minutes after subcutaneous injection of atropin sulphate, 1/30 grain. The incidence of *c* in the jugular tracing is shown by the dotted lines. Ventricular automatism is present from R^1 to R^2. The ventricular rate is 60 per minute. Fig. 6 *b*.—Fifteen minutes after atropin injection. It shows several automatic beats; the ventricular rate is 60 per minute.

the second lead (Figure 7, *c*), there is a slight difference in the length of the diastolic pauses, an arhythmia apparently of sinus origin. There are several automatic beats (Fig. 7, *c*, R^2, R^3, R^4) in the second part of the same lead. The beats are again sequential in the third lead (Fig. 7, *d*). Three days later, February 25, an electrocardiogram, second lead only (Fig. 8, *a* and *b*), was taken, ten and fifteen minutes, respectively, after the subcutaneous injection of 1/30 grain of atropin sulphate. With the exception of slight sinus arhythmia,

the beats are rhythmical, the ventricular rate about 60 per minute. Twenty minutes after the injection, independent ventricular activity with approximately the same ventricular rate is present (Fig. 8, *c*). In the later tracings (Fig. 8, *d*, *e*) normal auriculoventricular sequence is reestablished. It is important to note that the idioventricular and sequential complexes are identical throughout. Subsequent electrocardiographic tracings, the last taken three months after the onset of the arhythmia, show that the latter has not recurred.

COMMENT

Abnormal cardiac mechanisms similar to this have been ascribed to various causes. When auricles and ventricles beat at such rates that

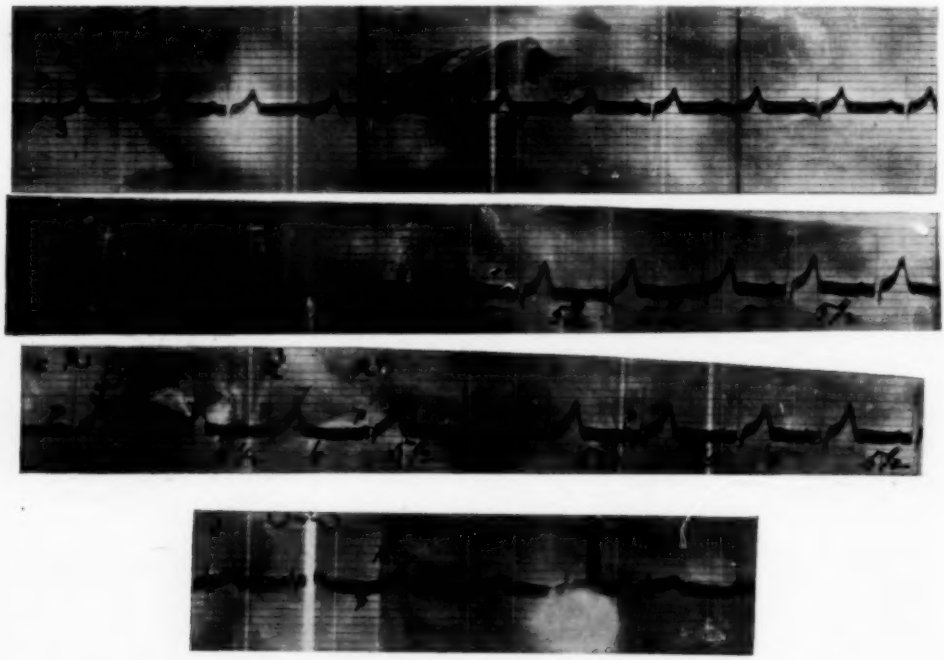

Fig. 7.—Electrocardiogram taken February 22. P = auricular deflection, R, S, T = ventricular complex. Fig. 7, *a*.—Lead 1 shows normal rhythm. Fig. 7, *b* and *c*.—Continuous parts of Lead 2. The numbers beneath the complexes represent the lengths of the beats in fifths of a second. Fig. 7, *b* shows slight sinus arhythmia. Fig. 7, *c*.—R^2, R^3 and R^4 are automatic ventricular contractions as shown by the varying P-R intervals. Slight sinus arhythmia is also present. Fig. 7, *d* (Lead 3).—The rhythm is again normal.

their waves and deflections in the tracings are regularly superimposed, their origin in or near the auriculoventricular node has sometimes been assumed; these are called nodal extrasystoles.[1] Such simultaneous

1. Lewis: Quart. Jour. Med., 1912-1913, vi, 221. Laslett: Ibid., vi, 210. Cowan, Fleming and Kennedy: Lancet, London, 1912, i, 207.

action is seen in parts of the tracings (Fig. 1, *a* and *b;* Fig. 8, *c*), but it apparently depends on *transient* identical auricular and ventricular speeds, for as the latter vary, varying *a-c* and *c-a,* or P-R intervals soon occur. Besides, nodal beats are usually either regularly interpolated in the normal rhythm, or when premature, are followed after longer or shorter compensatory pauses by the normal dominant beat,

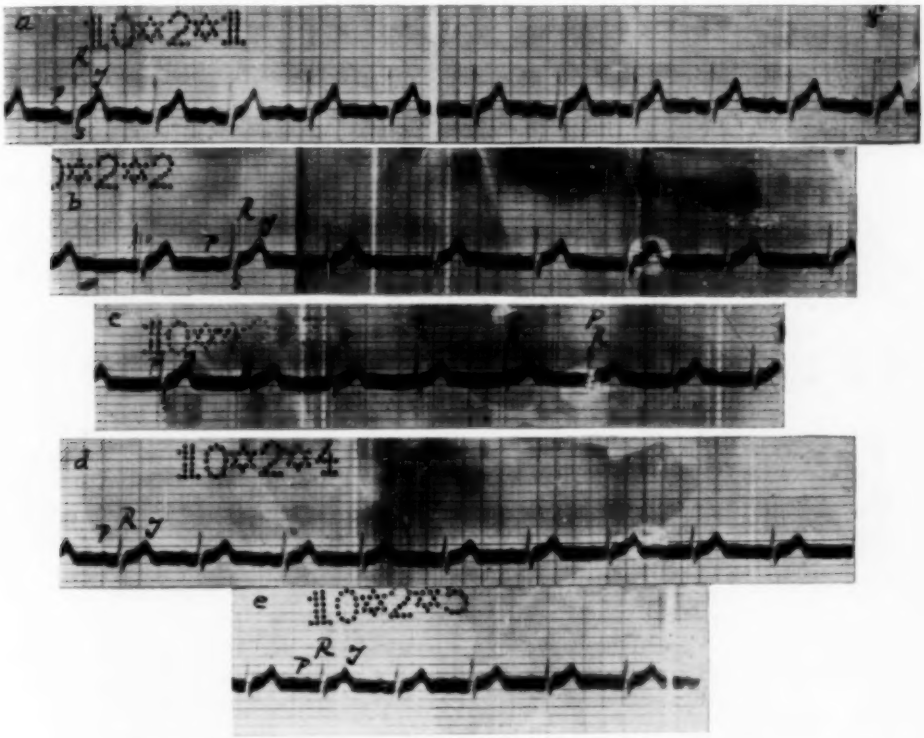

Fig. 8.—Taken February 25. Lead 2; sections taken after the subcutaneous injection of atropin sulphate, 1/30 grain. The time marker measures one-fifth second. Figure 8, *a* and *b*.—Ten and fifteen minutes, respectively, after atropin injection. Slight sinus arhythmia is present; the ventricular rate is about 60 per minute; the auriculoventricular sequence is normal. Fig. 8, *c*.—Twenty minutes after the injection. It shows ventricular automatism, with decreasing P-R intervals and finally simultaneous action of auricle and ventricle (superposition of P and R). Fig. 8, *d* and *e*.—Twenty-five and thirty-five minutes, respectively, after atropin. The beats are again sequential.

assumptions apparently not warranted by the electrocardiograms, all of whose complexes are alike. Retrograde conduction from ventricle to auricle, a rare reversal of the cardiac mechanism,[2] requires consider-

ation as a possible explanation. In the clinical case[2] described, the rhythm when established showed a definite ventriculo-auricular conduction time similar to the normal, and was accompanied by marked ventricular slowing. This conception if applied to my case would necessarily also assume that the reversed mechanism suddenly and irregularly ceased from time to time in such sections of the tracings which do not show a retrograde conduction time (*c-a* or R-P intervals) of less than one-fifth second, and that frequently occasional isolated beats were retrograde — assumptions which seem highly improbable and are not warranted by the tracings. Rihl[4] describes a case of occasional automatic ventricular action produced by vagal pressure. Lewis[5] reports a case of rheumatic mitral stenosis with decompensation; digitalis had been given with consequent ventricular automaticity ("ventricular escape," Lewis). Gallavardin, Dufourt and Petzetakis[6] describe three cases with slow pulses (in one case the rate was 36 per minute) in which there was no clinical evidence of organic cardiovascular disease. Numerous polygraphic and electrocardiographic tracings show the spontaneous occurrence of ventricular automatism in two cases; in all three it was readily evoked by ocular and vagus pressure and by atropin injection. They suggest two main causes for the phenomena: relative retardation of the auricular as compared with the idioventricular rate, or acceleration of the latter beyond the former. Two of their cases had very slow auricular rates occurring either spontaneously or induced by the methods described; the third showed no auricular retardation on vagus or ocular pressure, or after atropin injection. The arhythmia in the first two cases was apparently due to relatively increased idioventricular rapidity beyond that of the sinus. Except for a very slight change in the complexes of the automatic ventricular beats in two of the cases — the absence of a very small S wave — all of the complexes are identical. In digitalis poisoning, Cohn and Fraser[7] have occasionally found either identical auricular and ventricular speeds or ventricles beating more rapidly than auricles with ventricular escape. In my case there is at no time any marked pulse retardation — the lowest rate is 55 — nor is there any evidence of definite auricular slowing, though there is at the periods of ventricular automatism some difference, always slight, between auricular and ventricular rapidity. Except for occasional somewhat slower beats,

2. Cohn, Kessel and Mason: Heart, 1911-1912, iii, 321.
3. Williams and James: Heart, 1913-1914, v, 109.
4. Rihl: Deutsch. Arch. f. klin. Med., 1904, xciv, 286.
5. Lewis: Quart. Jour. Med., 1908-1909, ii, 356.
6. Gallavardin, Dufourt and Petzetakis: Arch. d. mal. du cœur, 1914, i, 1.
7. Cohn and Fraser: Internat. Med. Cong., 1913, Section 6, Part 2, p. 258.

the idioventricular and normal ventricular rates are approximately the same. Slight sinus arhythmia is sometimes present, but is not more marked than is frequently found as a physiological phenomenon.

As possible causes for the production of automatic ventricular action, neurogenic, toxic and organic factors require consideration. A neurogenic factor in the sense of a so-called neurosis due to extracardial conditions (for example, gastric disorders) causing abnormal peripheral disturbances in the centripetal arm of a reflex arc can be here dismissed because of the type of the disease, its course and the definite completion of the arhythmia with the end of the rheumatic attack. Though the action of toxins is an extremely complicated one and to a great extent at present unknown, it seems to depend on their complicated chemical composition and on intricate chemical reactions taking place in the body. It has been pointed out that digitalis poisoning may produce ventricular escape. By analogy, it seems theoretically possible that a rheumatic toxin may also produce a similar arhythmia, though there is no clinical proof for the assumption. Regarding an organic cause for the arhythmia, it is recalled that the patient developed a loud systolic murmur at the apex, one week after the appearance of the arhythmia; the murmur remained for two days, then gradually disappeared. It also disappeared when auricle and ventricle contracted simultaneously, an apparent corroboration that it was due to mitral insufficiency, organic or relative in nature. It is not my intention to discuss cardiac murmurs at any length, the etiology of many of which is not definitely known. Systolic apical murmurs which occur during the course of any febrile disease and then disappear without evidence of an organic cardiac lesion are by no means infrequent. On the other hand, organic murmurs usually increase in intensity and do not disappear. The occurrence of the murmur in conjunction with acute articular rheumatism makes its presence suspicious of some slight, possibly transient, valvular or myocardial involvement. Rheumatic infections cause myocardial inflammation in the form of submiliary myocardial nodules (Aschoff bodies). Healed or healing isolated Aschoff bodies have been found on the interventricular septum in hearts which were the subjects of rheumatic reinfection;[8] during their inflammatory state, if situated close to or even partly involving the bundle of His, before its division, they may conceivably cause sufficient local irritation to produce occasional ventricular automatism with beats of supraventricular origin, and yet the bundle need not be sufficiently compromised to prevent the idioventricular impulse from following its normal course in the conduction system — a fact which probably

8. Thalhimer and Rothschild: Jour. Exper. Med., 1914, xix, 417.

accounts for identical electrocardiographic complexes of all beats, rhythmic and arhythmic.

Right and left vagus pressure had no effect on auriculoventricular sequence. One of the atropin experiments was followed by a number of independent ventricular contractions, with no marked difference between ventricular and auricular rates. This observation does not necessarily exclude the possibility of an organic cause for ventricular automatism because an irritative lesion which does not entirely and permanently compromise the bundle may upset the normal nerve control and mechanism and make it susceptible to atropin poisoning. It would thus seem that the automatic ventricular mechanism was not sufficiently sensitive to respond to vagus pressure, but that atropin poisoning prevented the inhibitory vagus control and permitted ventricular escape.

SUMMARY AND CONCLUSIONS

A case of independent ventricular activity is described. The lowest ventricular rate is 56 per minute, the usual rate is 60 and remains so whether ventricular automatism is present or not. The electrocardiographic complexes of all beats are identical. At one time atropin injection is followed by ventricular escape. The occurrence of the automatic activity during the course of acute articular rheumatism and its disappearance later and a study of the physical signs make it possible that a small transient myocardial inflammatory focus at or near the auriculoventricular connections is the irritative cause of the abnormal mechanism.

Transient independent ventricular activity may occur with no change in the path followed by the idioventricular impulse, with no difference of rate between normal and abnormal beats, and with no marked retardation of the auricular rate.

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BOOK REVIEWS

DISEASE AND ITS CAUSES. By W. T. Councilman, Harvard University. New York: Henry Holt & Co.

The preface of this volume states that the author has endeavored to portray diseases as life under unusual conditions. The chapters on inflammation, cell growth, and the origin of tumors state clearly what is known on these subjects without going into unnecessary theories. The causes of infectious diseases are considered historically. Many illustrations are given of the discovery of pathogenic organisms by means of careful observation, experimentation and reasoning. The increase of disease in modern industrial life is emphasized as a check on the elimination of disease by the agencies of preventive medicine.

The book, though written for the general reader, may be read with great profit and enjoyment by the physician, for it is a philosophical as well as a scientific treatise on the most fascinating branch of medicine.

BLOOD-PRESSURE: ITS CLINICAL APPLICATIONS. By George William Norris, A.B., M.D. Lea & Febiger, Philadelphia and New York, 1914.

Dr. Norris's book on blood-pressure is certainly the best work on that subject in English up to date. The chapter on physiology of blood-pressure, contributed by Dr. J. Harold Austin, is an admirable summary of knowledge on that point. The account of the different instruments for measuring blood-pressure is full and clear. In fact, this account seems rather unnecessarily full; doubtless Dr. Norris felt that he would be accused of partizanship if he did not describe and picture almost all the instruments now in the market. But it appears that the time has come when such an accusation must be risked, and it is to be hoped that future books on this subject will not describe more than two or three instruments, including the ones the author finds most valuable.

The chapters on clinical aspects of blood-pressure measurement are admirable, although on page 182 the arrangement and labeling of matter is not altogether satisfactory. Possibly, too, somewhat less space might be given to the blood pressure findings in diseases in which they are really of no value. Doubtless, however, this sort of tabulation is more important in the present stage of our knowledge than it will be later on. Especially judicial and satisfactory is the account of functional tests, including both blood-pressure measurements and other methods in the study of functional efficiency of the circulation in Chapter V.

THE MENTAL HEALTH OF THE SCHOOL CHILD. By J. E. Wallace Wallin, Ph.D. Price $2. New Haven: Yale University Press, 1914.

This book consists of a series of lectures and papers which have been given by the author at various times and in various places. The subject is taken up very thoroughly and contains not only a scientific consideration, but also much data in regard to the state of psycho-educational movement in this country, especially as it affects the universities and medical schools.

It distinguishes also the position in education which is taken by psychological clinics. It lays emphasis on the fact that one must be specially trained and specially endowed temperamentally to take up this intricate study with any hope of success. One is struck with the sane ideas expressed in regard to the relative position of eugenics and the scientific consideration of the welfare of the race. The author has gone extensively into the subject of the effects of physical handicaps on the mental condition.

The book ends with a chapter on a scheme for clinical study of mentally and educationally unusual children. Taken as a whole this book is an excellent treatise on the subject and worth while, not only to one who is deeply interested in the mental health of the school child, but also to one who wishes to get an unbiased opinion of the present state of scientific attainments in this line.

PROBLEMS OF GENETICS. By William Bateson, M.A., F.R.S. With illustrations. Price $4; postage twenty-two cents. New Haven: Yale University Press, 1913.

Physicians are traditionally familiar with the study of nature. The present work shows how difficult it is for the medical man to keep up with the broad and rapid current of biologic investigation, yet it impresses on the reader the fact that more than ever, with problems of genetics thrust on the physician by the patient and the lawmaker, it is necessary to keep up as much as possible, if not by actual work, then by reading or otherwise. The style of the author is by no means easy, yet careful reading will disclose many suggestions of value. The medical mind as readily falls into routine as others, and one evidence of this is the acceptance of early evolutionary doctrines as of apodictic certainty. Bateson gives a rude shock to such minds. He begins by a discussion of genetics and the problem of species and varieties, based largely on his previous work on Mendelian principles of heredity. For those who have not followed Bateson's articles in the periodic press, this chapter is full of suggestions and stimulation, though minds that require dogma (in Bateson's words, those not "of first-rate analytical power") will be sadly disappointed. In the chapter on "Meristic Phenomena" many problems that appeal to the pathologist and clinician are touched on — not with finality, but again suggestively, for instance, in regard to twins, transposition, coalescence of digits, polydactylia, etc. In the classification of variations Bateson discusses the causes of acquired characteristics; that is, antibody formation, genius, etc. His views have become well known through other sources and are here clearly set forth. The chapter on the "Mutation Theory" should be studied by all who have floated with the evolutionary tide — not to follow another prophet, but to learn some of the things that still remain unknown. Altogether the work is one of great interest. Medical readers will appreciate it all the more, because in typography and other make-up it is so superior to their usual reading matter.

A TEXT-BOOK OF MEDICAL DIAGNOSIS. By James M. Anders, M.D., Ph.D., LL.D., and L. Napoleon Boston, A.M., M.D. Philadelphia and Boston: W. B. Saunders Company, 1914.

The "Text-Book of Medical Diagnosis" of Anders and Boston is one of the most faulty works on the subject that has ever come to the attention of the present reviewer. One can hardly open it anywhere without finding gross mistakes. The present reviewer has opened it twenty-six times at random, and finds the following twenty-six errors:

On page 101 it is stated that the sputum of bronchiectasis is usually "grayish or brown in color and mucopurulent in consistence." In fact, such sputum is rare in that disease. Pure pus is the rule.

On page 243 we are given, under the heading of "Laboratory Diagnosis of Pericarditis," a summary of the urinary changes seen in *any* fever, and therefore of no diagnostic value in pericarditis.

The picture on page 259, showing where a thrill was felt under the left clavicle a year after an attack of ulcerative endocarditis, is accompanied by no text which gives us any reason to believe that the ordinary subclavian thrill has been excluded.

On page 283 it is stated that the transmission of a loud mitral regurgitant murmur to the region of the left scapular angle is rare. Yet, on the opposite page, 282, it is stated that this murmur is found posteriorly.

On page 298 it is stated that in typical cases of chronic myocarditis the pulse is slow, from 30 to 60 beats per minute. Clinical observation gives no support for such a statement.

On page 351 primary anemia is wrongly defined as one in which the blood-making organs are affected primarily.

On page 385 it is stated that "drug purpura follows the administration of lethal doses of mercury, belladonna, potassium iodid, ergot," etc. Presumably "lethal" is a mistake for "toxic." Two paragraphs further down arthritic purpura is said to be associated with lesions "of the heart and other serous membranes."

On the next page, 386, it is said quite mistakenly that the blood findings in purpura closely resemble those seen in the various types of secondary enemia. In fact, the blood is usually normal in purpura. At the foot of this page it is stated that purpura of whatever type is always of grave significance; the grounds for such a statement the reviewer cannot conceive.

On page 490 the summary of the diagnostic characteristics of chronic gastritis contains nothing that is in any way peculiar to that disease or diagnostic of it.

On page 492 it is stated that the pain of gastric ulcer begins from one to ten minutes after the taking of food. Clinical experience is united in finding that the pain usually originates much later after the taking of food.

On page 498 it is stated that a lack of success in the attempt to remove fluid from the stomach by means of the stomach-tube is a characteristic feature of hour-glass contraction of the stomach. Of course this feature is not characteristic of hour-glass stomach, since it occurs in a variety of other conditions.

On page 501 it is incorrectly stated that secondary anemia is a constant feature of gastric cancer.

On page 506 it is stated that succussion sounds are to be found over the normal stomach of the negro. The African race enjoys no monopoly of this finding, as would seem to be implied.

On page 598 it is stated that in the early stages of atrophic cirrhosis the liver is somewhat enlarged. Possibly this may be true in some cases, but the reviewer knows of no evidence that bears out such a statement.

On page 624, under the diagnosis of pancreatic cancer, it is stated that the vomitus is "bilious" in character and that the stools contain undigested muscle fibers. In the reviewer's experience neither of these features is of any importance in the diagnosis of that disease.

On page 627 it is mistakenly stated that pronounced enlargement of the spleen is found in tricuspid regurgitation.

On page 734 it is said that the skin of patients with chronic dysentery always feels cool. This is certainly a misstatement. On the same page the presence of tubercle bacilli in the sputum is mentioned as a differential point between chronic dysentery and tuberculous ulceration of the colon. No hint is given of the fact that tubercle bacilli are often found present in the feces despite a normal condition of the intestine.

On page 805 mensuration is said to show deficient expansion of the phthisical chest even in the earliest cases — a remarkable statement. The further description of incipient phthisis corresponds properly with that of *advanced* phthisis, not of the incipient disease.

On page 807 it is stated that all traces of the ophthalmotuberculin reaction disappear from the conjunctivae within two or three days; the cases in which a much more serious conjunctivitis follows are here ignored.

On page 813 it is said that the hemic changes of tuberculosis are those of secondary anemia; there is no hint of the fact that the blood of advanced tuberculosis usually shows no anemia at all.

On page 892, under the etiology of acute articular rheumatism, nothing is said concerning the work of Poynton and Paine, or of Rosenow, on the peculiar

streptococci found by them in rheumatism, and now generally admitted to be the cause of that disease.

On page 894 the ancient fallacy of an "acid sweat" in acute articular rheumatism crops up once more. This is a relic of the old uric acid theory of rheumatism. In fact, the sweat of practically every febrile disease is acid unless the skin is previously cleansed with alcohol.

Under the account of tabes dorsalis the reviewer can find nothing about the diagnostic value of lumbar puncture.

On page 1009 occurs a quite antediluvian paragraph on lithemia.

On page 1152 we find myxedema strangely placed among the diseases of the nervous system, and arthritis deformans on page 1158 under the same general caption.

The foregoing twenty-six comments represent the results of opening this book in twenty-six places. The best thing in the book is Dr. George E. Pfahler's section on x-ray evidence in disease of the pericardium, heart and blood-vessels